VOLUME 109

JANUARY 15

1990

AMERICAN JOURNAL OF OPHTHALMOLOGY

Monthly since 1884

- ORIGINAL ARTICLES

Neonatal Herpes Simplex Virus Infection
el Azazi, Malm, Forsgren

Diagnosis of Experimental Herpes Simplex Keratitis
Lee, Storch, Reed, Hagerty, Pepose

Orbital Myositis With Lyme Disease
Seidenberg, Leib

Granular Epithelial Keratopathy
Rosenfeld, Mandelbaum, Corrent, Pflugfelder, Culbertson

Traumatic Hyphema
Spoor, Kwitko, O'Grady, Ramocki

Management of Recurrent Retinal Detachment
Sheta, Hida, McCuen

Subretinal Hemorrhage
Bennett, Folk, Blodi, Klugman

Drusen in Age-Related Macular Disease
Pauleikhoff, Barondes, Minassian, Chisholm, Bird

Congenital Stationary Night Blindness
Noble, Carr, Siegel

Visual Function and Retinal Leukocyte Velocity in Glaucoma
Sponsel, DePaul, Kaufman

Contact B-Scan Echography
Darnley-Fisch, Byrne, Hughes, Parrish, Feuer

Intraocular Pressure Management
Panek, Boothe, Lee, Zemplenyi, Pettit

Complications of Malpositioned Jones Tubes
Bartley, Gustafson

Class II Antigen Expression
Baudouin, Gordon, Fredj-Reygrobellet, Baudouin, Peyman, Gastaud, Bazan

Auditory Function in Duane's Retraction Syndrome
Ro, Chernoff, MacRae, Orton, Cadera

Infantile Esotropia
Keech, Scott, Baker

Subepidermal Calcified Nodules
Ferry

- EDITORIAL

Variations in Patient Care to Identify Preferred Management
Sommer

- LETTERS TO THE JOURNAL

Corneal donors and human immunodeficiency virus
Hwang, Ward, Trousdale, Smith

Interferon treatment of keratitis
McLeish, Pflugfelder, Crouse, Rabinowitz, Miller, Hill, Atherton

Herpes simplex and epithelial defects after keratoplasty
Beyer, Byrd, Hill, Kaufman

***Neisseria cinerea* acute purulent conjunctivitis**
Au, Reynolds, Rambin, Mahjoub

Corneal defect and *Listeria monocytogenes*
Eiferman, Flaherty, Rivard

Storage of tissue plasminogen activator
Ward, Weck

Corticosteroid-responsive optic neuropathy
Lam, Weingeist

Ophthalmomyiasis in an eyelid reconstruction
Bosniak, Schiller

Subcutaneous fat atrophy after corticosteroid injection
Townshend, Buckley

Orbital pseudotumor with hemorrhage
Linberg, Mayle

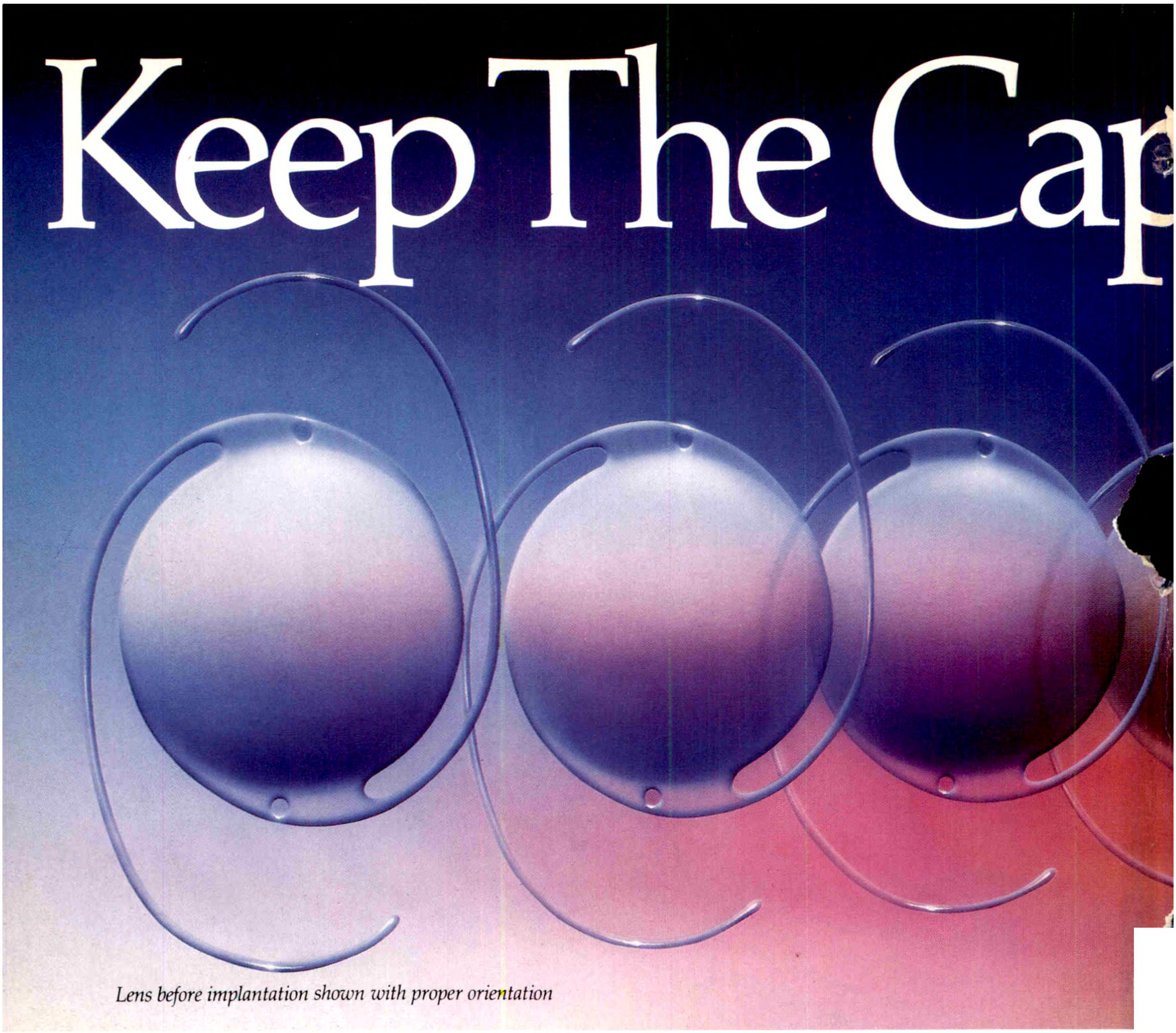
Ocular flutter in vidarabine toxicity
Gizzi, Rudolph, Perakis

Retinal artery occlusion
Greven, van Rens, Slusher

Laser therapy using +90-D lens
Bartov, Treister

Measurement of retinal images
Arzabe, Jalkh, Fariza, Akiba, Quiroz

AJO®



Lens before implantation shown with proper orientation

By conforming, not deforming.

Bag Conformity and Centration. The two features of CILCO® cantilever loop single-piece IOLs that provide for better capsular fit.

Their proprietary haptic designs allow these lenses to accommodate to the size of the capsular bag. This conformity can eliminate the unequal zonular stress and the capsular bag distortion that can occur with an exceptionally long haptic, or unforgiving haptic design. The ability to accommodate also decreases the likelihood of a haptic overextending the anterior capsular flap and displacing into the sulcus.

Our unique haptic designs result in uniform radial forces that automatically center the optic. These gentle forces of centration also restore the natural shape of the capsular bag. This is achieved by providing an effective 360 degrees of radial stretch. And, this stretch helps to eliminate capsular wrinkles, a primary pathway for posterior capsule opacification.

Manufactured from lathe-cut, high molecular weight PMMA, these lenses exhibit superior memory. Thus, they preserve the angulation that minimizes the risk of

AJO® AMERICAN JOURNAL OF OPHTHALMOLOGY®

ISSN 0002-9394 January 1990 Series 3, Vol. 109, No. 1

GENERAL INFORMATION

Address typescripts to Frank W. Newell, M.D., Editor, American Journal of Ophthalmology, Suite 1415, 435 North Michigan Avenue, Chicago, IL 60611.

Manuscripts must be original material submitted solely to The American Journal of Ophthalmology. Two copies must be submitted; the second copy may be machine-duplicated. The entire manuscript, including case reports, footnotes, and references, must be typed double-spaced, with 1½-inch margins, on 8½ by 11-inch heavy white bond paper. See Instructions to Authors published elsewhere in this issue. Copies of Instructions to Authors will be mailed on request. All manuscripts originating in the United States must be sent by first-class mail; those manuscripts originating outside the United States must be sent airmail. Receipt of manuscript is acknowledged immediately. Edited typescripts sent to the author must be corrected and returned within 24 hours to Manuscript Editor, American Journal of Ophthalmology, Suite 1415, 435 North Michigan Avenue, Chicago, IL 60611.

At the time of submission, a copyright transfer, published monthly in The American Journal of Ophthalmology, signed by each of the authors must be included with the typescript. No article or letter will be reviewed until the signed copyright transfer is received.

Manuscripts submitted for consideration are reviewed by members of the Editorial Board and other experts in the field. An unpublished manuscript is a privileged document that must be protected from any form of exploitation. The reviewer should not cite the manuscript or refer to the work it describes before it has been published. Reviewers must refrain from using the information contained in the manuscript for the advancement of their own work, their colleagues' work, or their institution's work. Reviewers are consultants to the editor and are instructed not to discuss the paper with the authors. Reviewers work anonymously and their identity may not be revealed to authors or to others.

Permission to reprint any portion of published articles must be obtained in writing from both the Ophthalmic Publishing Company and from the authors of the articles.

Reprints may be obtained from Ophthalmic Publishing Company, Suite 1415, 435 North Michigan Avenue, Chicago, IL 60611, if ordered at the time the typescript is returned.

Address news items and society proceedings to News Editor, American Journal of Ophthalmology, Suite 1415, 435 North Michigan Avenue, Chicago, IL 60611.

Exchange copies of medical journals should be sent to David Shoch, M.D., Suite 1415, 435 North Michigan Avenue, Chicago, IL 60611.

Subscriptions: Subscriptions, requests for single issues, notices of change of address, advertising and other communications should be sent to Ophthalmic Publishing Company, Suite 1415, 435 North Michigan Avenue, Chicago, IL 60611. Notices of change of address must be received at least 60 days in advance and must include both old and new addresses and AJO identification number.

Send claims for issues not received no later than two months after the issue date for domestic and Canadian subscribers and four months after the issue date for all other foreign subscribers. Address claims to Circulation Coordinator, Ophthalmic Publishing Company, Suite 1415, 435 North Michigan Avenue, Chicago, IL 60611.

Advertising: Insertion orders, copy, and materials should be sent to the Media Planner and must be received by the 20th of the second preceding month that the advertisement is scheduled. Consult the Media Planner for extensions, rates, and media kits at The American Journal of Ophthalmology, Suite 1415, 435 North Michigan Avenue, Chicago, IL 60611; telephone (312) 787-3853; FAX (312) 787-5186.

The American Journal of Ophthalmology is published monthly by the Ophthalmic Publishing Company, Suite 1415, 435 North Michigan Avenue, Chicago, IL 60611. The subscription rates in the United States are as follows: one year, $48.00, two years, $90.00. In Canada and all other foreign countries, the rates are as follows: one year, $75.00; two years, $140.00; paid in U.S. bank draft or international money order. Single issues are available for $10.00 in the United States and for $13.00 in all other countries. Subscription and Advertising Office: Ophthalmic Publishing Company, Suite 1415, 435 North Michigan Avenue, Chicago, IL 60611.

AJO® AMERICAN JOURNAL OF OPHTHALMOLOGY®

ISSN 0002-9394 January 1990 Series 3, Vol. 109, No. 1

TABLE OF CONTENTS

ORIGINAL ARTICLES

Late ophthalmologic manifestations of neonatal herpes simplex virus infection
Mildred el Azazi, Gunilla Malm, and Marianne Forsgren . . . 1

Comparative laboratory diagnosis of experimental herpes simplex keratitis
Steven F. Lee, Gregory A. Storch, Charles A. Reed, Colleen M. Hagerty, and Jay S. Pepose . . . 8

Orbital myositis with Lyme disease
Keith B. Seidenberg and Martin L. Leib . . . 13

Granular epithelial keratopathy as an unusual manifestation of *Pseudomonas* keratitis associated with extended-wear soft contact lenses
Steven I. Rosenfeld, Sid Mandelbaum, George F. Corrent, Stephen C. Pflugfelder, and William W. Culbertson . . . 17

Traumatic hyphema in an urban population
Thomas C. Spoor, Geoffrey M. Kwitko, John M. O'Grady, and John M. Ramocki . . . 23

Cyanoacrylate tissue adhesive in the management of recurrent retinal detachment caused by macular hole
Sherif M. Sheta, Tetsuo Hida, and Brooks W. McCuen II . . . 28

Factors prognostic of visual outcome in patients with subretinal hemorrhage
Steven R. Bennett, James C. Folk, Christopher F. Blodi, and Marie Klugman . . . 33

Drusen as risk factors in age-related macular disease
D. Pauleikhoff, M. J. Barondes, D. Minassian, I. H. Chisholm, and A. C. Bird . . . 38

Autosomal dominant congenital stationary night blindness and normal fundus with an electronegative electroretinogram
Kenneth G. Noble, Ronald E. Carr, and Irwin M. Siegel . . . 44

Correlation of visual function and retinal leukocyte velocity in glaucoma
William E. Sponsel, Kathleen L. DePaul, and Paul L. Kaufman . . . 49

Contact B-scan echography in the assessment of optic nerve cupping
Deborah A. Darnley-Fisch, Sandra Frazier Byrne, J. Randall Hughes, Richard K. Parrish II, and William J. Feuer . . . 55

Intraocular pressure measurement with the Tono-Pen through soft contact lenses
William C. Panek, William A. Boothe, David A. Lee, Eva Zemplenyi, and Thomas H. Pettit . . . 62

Complications of malpositioned Jones tubes
George B. Bartley and Ray O. Gustafson . . . 66

Class II antigen expression in diabetic preretinal membranes
Christophe Baudouin, William C. Gordon, Daniele Fredj-Reygrobellet, Francoise Baudouin, Gholam Peyman, Pierre Gastaud, and Nicolas G. Bazan . . . 70

Auditory function in Duane's retraction syndrome
A. Ro., G. Chernoff, D. MacRae, R. B. Orton, and W. Cadera . . . 75

The medial rectus muscle insertion site in infantile esotropia
Ronald V. Keech, William E. Scott, and John D. Baker . . . 79

Subepidermal calcified nodules of the eyelid
Andrew P. Ferry . . . 85

EDITORIAL

Variations in patient care to identify preferred management
Alfred Sommer . . . 89

LETTERS TO THE JOURNAL

Human immunodeficiency virus seroprevalence among potential corneal donors from medical examiner cases. *David G. Hwang, Donald E. Ward, Melvin D. Trousdale, and Ronald E. Smith,* **92. Interferon treatment of herpetic keratitis in a patient with acquired immunodeficiency syndrome.** *William McLeish, Stephen C. Pflugfelder, Cecelia Crouse, Stephen Rabinowitz, Darlene Miller, Edgar L. Hill, and Sally Atherton,* **93. Herpes simplex virus and persistent epithelial defects after penetrating keratoplasty.** *Craig F. Beyer, Thomas J. Byrd, James M. Hill, and Herbert E. Kaufman,* **95. *Neisseria cinerea* acute purulent conjunctivitis.** *Yue-Kong Au, Mark D. Reynolds, Ellen D. Rambin, and Salah B. Mahjoub,* **96. Persistent corneal defect caused by *Listeria monocytogenes*.** *Richard A. Eiferman, Kevin T. Flaherty, and Arthur K. Rivard,* **97. Dilution and storage of recombinant tissue plasminogen activator (Activase) in balanced salt solutions.** *Carole Ward and Suzanne Weck,* **98. Corticosteroid-responsive traumatic optic neuropathy.** *Byron L. Lam and Thomas A. Weingeist,* **99. Ophthalmomyiasis in an eyelid reconstruction.** *Stephen L. Bosniak and Jeffrey D. Schiller,* **101. Linear subcutaneous fat atrophy after a single corticosteroid injection for ocular adnexal hemangioma.** *Lois M. Townshend and Edward G. Buckley,* **102. Spontaneous orbital hemorrhage associated with idiopathic inflammatory pseudotumor.** *John V. Linberg and Mark*

(Table of Contents continued on Advertising Page 8)

NEW

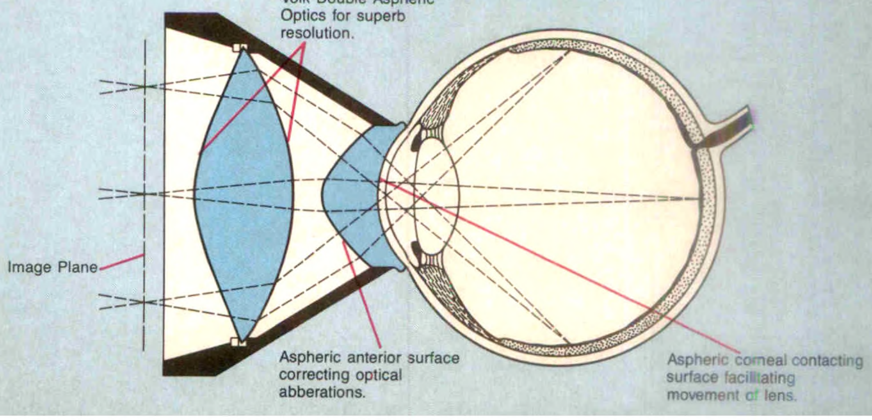
Volk QuadrAspheric Fundus Lens®

The Volk QuadrAspheric Fundus Lens® utilizes a new concept in diagnostic/therapeutic contact lens design, with FOUR aspheric surfaces for superior fundus viewing!

Each surface has an exact aspheric curvature providing overall performance far exceeding that of diagnostic contact lenses of similar design.

- Superb resolution.
- Super wide 130° field of view.
- Aspheric corneal contacting surface for superior fit.
- High efficiency multi AR coating.
- All these outstanding optical and performance features in a light weight, compact, and comfortable design.

Patent Pending



VOLK
The Leader in Aspheric Optics

7893 Enterprise Drive, Mentor, Ohio 44060
Phone: (216) 942-6161
Fax: (216) 942-2257

VISIT US AT BOOTH #32
AT THE CLAO MEETING IN LAS VEGAS

AJO® AMERICAN JOURNAL OF OPHTHALMOLOGY®

ISSN 0002-9394 | January 1990 | Series 3, Vol. 109, No. 1

TABLE OF CONTENTS *(continued from Advertising page 6)*

Mayle, **103. Ocular flutter in vidarabine toxicity.** *Martin Gizzi, Steven Rudolph, and Anthony Perakis,* **105. Branch retinal artery occlusion after platelet transfusion.** *Craig M. Greven, Erik van Rens, and M. Madison Slusher,* **105. Laser treatment of the retinal periphery with the +90-diopter lens.** *Elisha Bartov and Giora Treister,* **107. A simple device to standardize measurements of retinal structures in fundus photographs and retinal angiograms.** *Carlos W. Arzabe, Alex E. Jalkh, Enrique Fariza, Jun Akiba, and Miguel A. Quiroz,* **107.**

CORRESPONDENCE

Test-retest variability in glaucomatous visual fields. *Jody R. Piltz and Richard J. Starita,* **109. Reply.** *Anders Heijl, Anna Lindgren, and Georg Lindgren,* **110. Timolol-pilocarpine combined vs timolol and pilocarpine given separately.** *Orna Geyer, Leonard Rothkoff, and Moshe Lazar,* **111. Reply.** *Mats B. Söderström, Per-Arne Granström, Örjan Wallin, and William Thorburn,* **111.**

BOOK REVIEWS

Intraocular Lenses. Evolution, Designs, Complications, and Pathology (David J. Apple, Nick Mamalis, Randall J. Olson, and Marilyn C. Kincaid). *Reviewed by Hans E. Grossniklaus,* **112. Clinical Anatomy of the Eye (Richard Snell and Michael A. Lemp).** *Reviewed by Gerhard W. Cibis,* **112. Ophthalmology. A Diagnostic Text (William H. Coles), 113. Ophthalmology. What Shall I Do? (Jack J. Kanski and Bev Daily), 113.**

ABSTRACTS 115

NEWS ITEMS 119

CLASSIFIEDS .... Begins on Advertising 51

COPYRIGHT TRANSFER .... Advertising 30

CURRENT ISSUE SUMMARIES .... Begins on Advertising 20

INSTRUCTIONS TO AUTHORS .... Advertising 33

NEW PRODUCTS AND SERVICES .... Begins on Advertising 40

ADVERTISING INDEX .... Advertising 55

AMERICAN JOURNAL OF OPHTHALMOLOGY®

VOLUME 109 NUMBER 1 JANUARY, 1990

Late Ophthalmologic Manifestations of Neonatal Herpes Simplex Virus Infection

Mildred el Azazi, M.D., Gunilla Malm, M.D., and Marianne Forsgren, M.D.

We examined 32 children one to 15 years after virologically verified neonatal herpes simplex virus infection. Sixteen of 17 (94%) neurologically impaired children had ocular abnormalities compared to three of 15 (20%) neurologically healthy children. Disturbed oculomotor control occurred in 14 children (44%), most of whom were among those with severe handicap. Ocular morbidity was present in 13 (40%) of 32 children: one had cataracts, two had corneal scars, seven had optic atrophy, and nine had chorioretinal scars. The clinically silent chorioretinal lesions were manifest as coarse hyperpigmented areas between the equator and ora serrata. One child had suffered from acute fulminant retinitis. Twelve of 13 (93%) severely handicapped children had impaired vision, mainly because of cortical blindness. Less affected children had normal vision unless corneal scars were present. Long-term observation of patients with neonatal herpes infections is essential because ocular manifestations are not rare, and recurrences may be more common than previously reported.

THE HERPES SIMPLEX VIRUS is an infectious agent that results in manifestations ranging from blisters to fatal encephalitis. Rare but devastating infections occur in the neonate, in whom 80% of infections are caused by type 2 herpes simplex virus.[1] Because the frequency of the genital herpes infections is increasing, the incidence of herpes simplex virus infections in the newborn may also be expected to rise.[2] Because genital herpes in the mother at term is often subclinical or not recognized, prevention is difficult.

The clinical manifestations of neonatal herpes include the following[3]: skin, eye, and mouth disease; central nervous system disease; and the disseminated form of the disease when visceral organs are affected. The latter two forms may also be accompanied by skin, eye, or mouth involvement. Despite antiviral therapy, the disseminated form and localized central nervous system disease have a mortality of approximately 57% and 10%, respectively,[4] and sequelae occur in survivors.

In the acute stage of the neonatal herpes infection, the most frequent ocular symptom is conjunctivitis, often coexisting with keratitis, which is the next most common symptom. After the acute phase, serious complications such as necrotizing retinochoroiditis, cataracts, optic neuritis, and phthisis have been reported.[5] Because few long-term studies[6,7] have been carried out on late ophthalmologic manifestations of neonatal herpes simplex disease, a follow-up study was performed on patients one to 15 years after the infection. We found a much higher incidence of herpetic ocular manifestations than previously reported.[5,6]

Subjects and Methods

The records of 45 patients with virologically confirmed neonatal herpes were obtained from

Accepted for publication Oct. 20, 1989.

From the Departments of Ophthalmology (Dr. el Azazi) and Pediatrics (Dr. Malm), Huddinge University Hospital, Huddinge, and Department of Virology (Dr. Forsgren), Central Microbiological Laboratory, Stockholm County Council, Sweden. This study was supported in part by grants from the Samaritan Foundation and Erco Läkemedel AB.

Reprint requests to M. el Azazi, M.D., Department of Ophthalmology, Danderyds Hospital, S-182 88 Danderyd, Sweden.

the registers of four diagnostic virologic laboratories in Sweden (31 consecutive cases from the Central Microbiological Laboratory of Stockholm and National Bacteriological Laboratory in Stockholm, 1971 to 1986; 14 consecutive cases from the Departments of Virology in Malmö (General Hospital) and Gothenburg (University of Gothenburg), 1981 to 1986. Twelve children died, and the parents of one child refused ophthalmologic examination of their child. The 32 remaining children were examined by one of us (M.A.), except for two patients about whom information was obtained from the primary ophthalmologist. The distribution of type 1 and type 2 herpes simplex infections among the examined children is shown in Table 1, and mean age at examination is shown in the footnote. The medical treatment of the children between 1971 and 1986 had depended on the availability of antiviral drugs (vidarabine, cytosine arabinoside, and acyclovir) and had also included blood exchange, herpes hyperimmune globulin, and interferon. In some patients, no treatment had been given.

Visual acuity was assessed with Snellen charts, letter matching tests, preferential looking charts, or simpler tests, such as the ability to follow a penlight. The anterior segment and optical media were examined with a slit lamp when possible, and a magnifying lens was used in other patients. The fundus was examined by indirect ophthalmoscopy with the pupils dilated.

The examined children were divided into three groups according to the neurologic sequelae of the neonatal herpes simplex infection as follows: I, no apparent disease; II, mild neurologic disability or mental disability or both; and III, severe handicap.[8] A summary of the ophthalmologic findings in the three groups of children is shown in Table 2.

Group I consisted of 15 apparently healthy children of both sexes. Two of the patients had not been treated. Fourteen children had normal vision, and 12 had normal eyes. One 13-year-old girl had a unilateral reduction of visual acuity to 20/30 because of a central corneal scar, as well as posterior synechiae and sector-shaped iris atrophy from unilateral recurrent keratitis at the age of 3 years. This patient, treated systemically with 10 mg/day of cytosine arabinoside for a week, was diagnosed to have a strictured esophagus at the age of 1 year. One 2-year-old boy showed small, circumscribed areas of retinal atrophy with pigmented borders in the temporal equatorial regions of both fundi. Another 13-year-old girl had a small, circumscribed hyperpigmented spot in the nasal periphery of one eye. These three children had suffered from type 1 herpes simplex infections of the disseminated form.

Group II included four children with mild neurologic disability or mental retardation. One child had, at the age of 9 years, a reduction of visual acuity to 20/40 in the right eye and 20/30 in the left eye and residual corneal scars because of severe bilateral keratoconjunctivitis as part of a disseminated type 1 infection at the age of 8 days. Other sequelae in this child were exotropia, dissociated vertical deviation, and slight mental retardation. The other children had normal visual acuity. One boy, with a slight spastic hemiparesis after a type 2 meningoencephalitis, showed at the age of 10 years heavily hyperpigmented scars in the peripheral fundi (Figure). None of these children had any iris

TABLE 1

MORBIDITY DATA

	DISEASE (STATE OF HEALTH)*										
	CENTRAL NERVOUS SYSTEM			DISSEMINATED			SKIN, EYES, MOUTH				
	(I	II	III)	(I	II	III)	(I	II	III)	TOTAL	%
Herpes simplex virus type 2	7	3	10	0	1	1	3	0	1	26	81
Herpes simplex virus type 1	1	0	1	3	0	0	1	0	0	6	19
Total	8	3	11	3	1	1	4	0	1	32	100

*I indicates apparently healthy (mean age, 6 ± 5 years); II, mild neurologic or mental disability or both (mean age, 9 ± 3 years); III, severe neurologic and mental disability (mean age, 5 ± 4 years).

TABLE 2
OPHTHALMOLOGIC DATA

	DISEASE (STATE OF HEALTH)*										
	CENTRAL NERVOUS SYSTEM			DISSEMINATED			SKIN, EYES, MOUTH				
	(I	II	III)	(I	II	III)	(I	II	III)	TOTAL	%
Corneal scars	0	0	0	1	1	0	0	0	0	2	6
Cataract	0	0	0	0	0	1	0	0	0	1	3
Chorioretinal scars	0	1	5	1	0	1	1	0	0	9	28
Optic atrophy	0	0	5	0	0	1	0	0	1	7	22
Exotropia	0	1	8	0	1	0	0	0	1	11	34
Esotropia	0	0	1	0	0	0	0	0	0	1	3
Skew deviation	0	1	7	0	1	0	0	0	1	10	31
Tonic deviation	0	0	6	0	0	0	0	0	1	7	22
Visual acuity < 20/200	0	0	10	0	0	1	0	0	1	12	37

*I indicates apparently healthy (mean age, 6 ± 5 years); II, mild neurologic or mental disability or both (mean age, 9 ± 3 years); III, severe neurologic and mental disability (mean age, 5 ± 4 years).

atrophy or posterior synechiae. One 4-year-old girl with normal fundi had an alternating exotropia and dissociated vertical deviation of her eyes. Only one patient in group II was ophthalmologically normal. Two children had received antiviral treatment.

Group III consisted of 13 children who had developed severe neurologic handicaps after neonatal herpes simplex encephalitis, which in all cases but one were type 2–associated. Three children had not received treatment. All but one of the children were tetraplegic, and all were severely mentally impaired. None of the children was ophthalmologically normal. One girl with mental retardation had, at the age of 15 years, heavily pigmented chorioretinal scars inferiorly in both fundi and in the nasal upper periphery of the right eye. One 5-year-old boy

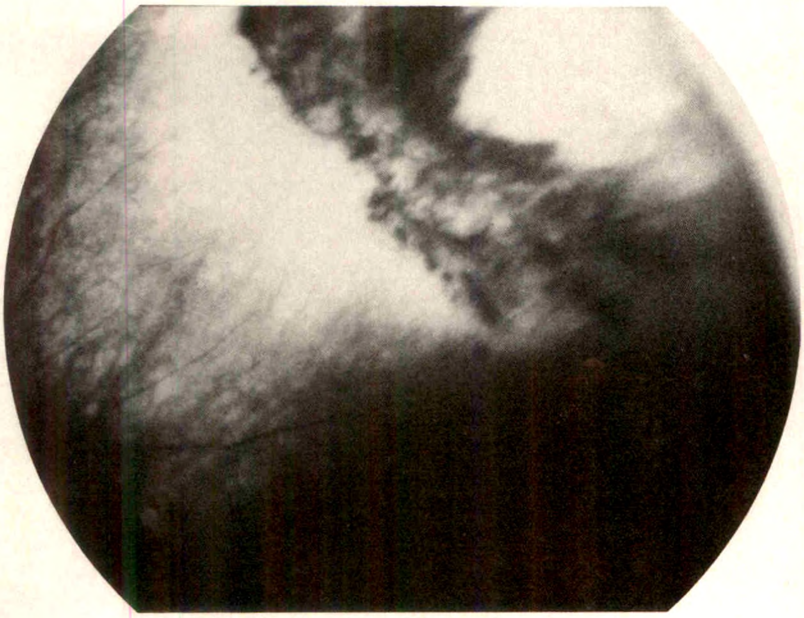


Figure (el Azazi, Malm, and Forsgren). Fundus of a 10-year-old boy with mild neurologic disability with clinically silent, pigmented, chorioretinal lesions in the nasal equatorial regions of both eyes and, as shown, in the upper temporal quadrant of the left eye.

was blind because of a bilateral necrotizing vitreoretinitis. He had cataracts, optic atrophy, and large retrolenticular calcifications. The visual acuity of the remaining children ranged from 20/400 to total blindness (usually of the cortical type) as tested with the preferential looking method. Six children had pale optic disks. Four of these children also showed pigmentary epithelial disturbances in their peripheral fundi. None of the children had macular lesions.

All but one of the children in group III demonstrated overt disturbances of ocular alignment and displayed various kinds of nystagmus. The eye movements of the amaurotic child were not assessed, except for the presence of nystagmus. Seven children demonstrated an intermittent conjugated tonic deviation in the horizontal plane. One child had additional convergent spastic movements. Nine children exhibited an intermittent large angle exotropia, and three of them had earlier been described as esotropic. Only one child showed an esotropia. Seven of these children demonstrated alternating skew deviation, that is, a reproducible vertical dissociation of their eyes during horizontal gaze movements, manifested as an upward torsion of the abducted eye and a simultaneous depression of the adducted eye when looking right or left. Ductions and versions did not suggest any ocular muscle palsy. Responses to oculocephalic maneuvers were not tested.

Ophthalmologic data could be extracted from the medical records of an additional three children with the encephalitic form of the neonatal disease. They had died between the ages of 8 months and 6 years. All had severe visual impairment, optic atrophy, as well as peripheral coarse retinal hyperpigmentation with some retinal atrophy; in one eye of one patient, the macula was affected. Two children had tonic gaze deviations. None had a history of uveitis or opacities of the media.

The ocular manifestations of neonatal herpes simplex virus disease have been well described by Nahmias and associates,[5,9,10] who concluded that ophthalmologic findings occurred in 51 (17%) of the 297 patients examined. They reported an incidence of conjunctivitis in 30 patients (10%), keratitis in 19 (7%), chorioretinitis or chorioretinal scarring in 13 (4.4%), cataract in three (1%), and optic atrophy in two (less than 1%). Their observations referred to the acute and immediate convalescent period, whereas this study addresses the late ophthalmologic sequelae. Even though the most common ocular herpetic manifestation, conjunctivitis, is not included in this study, the general ocular morbidity was found to be 40% (13 of 32 cases), which may be related to the increased findings of chorioretinal scarring in nine children (28%) and optic atrophy in seven children (22%). The incidence of phthisis, cataract, and corneal scarring after earlier keratitis did not differ from previous investigations. Our findings, which are in accordance with a recent study,[6] may partly reflect a decreased mortality of the disease with the advance of antiviral therapy, as well as a progression of the disease in the retina.

The incidence of corneal scars after previous keratitis in two children (6%) in our relatively small study agrees with that described in previous reports[5,6] on the acute corneal manifestation of the disease. This finding is unexpected because residual scars after acute keratitis are less common than the acute manifestation itself, and recurrent keratitis is rare. Recurrences may, however, occur years later, as in one of our patients. It is evident that useful vision may develop despite the sometimes dramatic appearance of an acute keratitis with totally opaque cornea because of diffuse epithelial and stromal involvement. The lowest visual acuity because of corneal scars was 20/40 in the patients in this study.

One patient in this study developed bilateral cataracts as a late complication of fulminant uveitis. The five cases of neonatal herpetic cataracts reported up to 1988[6,9,11-13] were all associated with previous chorioretinitis, and these cataracts developed several months after the acute phase, as in our patient.

The incidence of chorioretinal scars in nine children (28%) is similar to the observations in a recent study[6] and much higher than the previously reported incidence of acute retinitis.[5] In half of these earlier reported cases,[6,9,11,12,14-18] clinically inactive chorioretinal lesions were documented. The lesions were described as prominent hyperpigmented areas with discrete spots of retinal atrophy located between the equator and ora serrata, often bilaterally. This description is compatible with the retinal scars found in the patients in this study. Because there were no signs or history of antecedent uveitis in our patients or in those reported in the literature, it seems reasonable to assume that the initial herpetic retinal lesion was confined to the retinal pigment epithelium. Immunologic mechanisms and a restricted amount of the intraocular virus may confine the infection

to a mild involvement of the retinal pigment epithelium and prevent immediate development of acute fulminant retinitis. This ophthalmologic complication of neonatal herpes infection seems to be infrequent. Less than ten cases of active fulminant retinitis have been reported since 1952.[6,9,13,14,19-22] In our study, only one patient suffered from the sequelae of necrotizing retinitis.

The chorioretinal scars found at a higher rate than previously reported may indicate a long latency of the herpes virus infection within the retina. This may indicate that the patient is at risk for the later development of the acute retinal necrosis syndrome, as was recently observed in a 30-year-old woman (unpublished data).

The late appearance of the fundus lesions, usually found in children with encephalitis, may suggest that the virus gains access to the eye from the central nervous system. The obvious route would be the optic nerve or its sheaths. Animal studies of herpes simplex retinitis, however, have shown that viral spread from the brain to the eye may also occur despite transected optic nerves.[23] It is, therefore, tempting to suggest that the virus spreads intra-axonally in the ciliary nerves or by immune complexes by means of ciliary vessels, which could explain the peripheral location of the fundus lesions.

In animal studies, herpes simplex virus retinopathies can be induced by both types of the herpes simplex virus, whereas in human neonates the retinopathies have been considered to be exclusively type 2–associated.[5] In this study, however, we found two cases of chorioretinal scarring among the healthy children infected with type 1 herpes simplex virus, and one case of necrotizing type 1 retinitis has been reported earlier.[18]

The most severe visual impairment was found among the children with extensive brain damage, presumably caused by cortical blindness. In more than half of these children, who also had various degrees of optic atrophy, it was not possible to distinguish cortical blindness from visual deterioration caused solely by optic atrophy. Limited attention has been focused on the presence and pathogenesis of optic atrophy in neonatal herpes virus encephalitis.[5,10,13] Transsynaptic retrograde degeneration may occur in the immature visual pathway in patients with extensive destruction of the striate cortex, and this condition may be manifested as optic atrophy.[24] Because myelination of the posterior visual pathways starts at birth,[24] the visual system of premature infants may be particularly susceptible to this type of retrograde degeneration.

Whether or not the optic nerve itself is primarily involved in the neonatal herpetic infection is an open question. In the few published histopathologic[17,19] studies, inclusion bodies or virus particles were not found in the optic nerves, but were seen in the surrounding sheaths in association with opticochiasmatic arachnoiditis.[19]

In patients with coexistent severe retinal destruction, the optic nerve may be demyelinated by ascending (wallerian) degeneration.[24]

Animal studies of herpes simplex virus encephalopathies have shown that demyelination of herpes simplex virus–infected axons can occur in addition to the well-documented necrotizing changes.[25] This occurrence would result in optic atrophy regardless of affected neuronal level in the visual pathway, because transsynaptic degeneration may occur at this age.

The possibility that the optic atrophy was secondary to papilledema caused by increased intracranial pressure seems remote, considering the flexibility of the neonate's skull. Such a mechanism is contradicted by the propensity for brain atrophy of infants with herpetic encephalitis at this age, which later causes the characteristic microcephalic appearance of affected children. The exception in our study was a severely damaged child with normal skull size suffering from hydrocephalus caused by postinflammatory aqueduct stenosis.

The incidence of strabismus is higher among children with neurologic disorders than in the general population (2% to 4%). Corey and associates[6] verified this in a recent follow-up study: six of 23 children (23%) had strabismus at a mean age of 20 months, and most of the strabismic children were esotropic. In our study, strabismus occurred in ⅓ of the children (1 to 15 years old; mean age, 5 years), almost all of whom were exotropic. There was an overrepresentation of divergent strabismus among the children with severe neurologic sequelae. Our results do not contradict those of Corey and associates but merely emphasize the instability of the strabismic deviation, as well as the age-dependent tendency toward exodeviations in children with early brain damage. Most of our brain-damaged patients also demonstrated nystagmus, dissociated vertical eye movements, and tonic gaze deviations in mentioned order. Computed tomographic findings in neonatal herpetic encephalitis indicate extensive de-

struction of the cortical white matter throughout the hemispheres.[26] The strabismus and the tonic gaze deviations may therefore be caused by damage to the cortical oculomotor centers. The presence of alternating skew deviations and various forms of nystagmus, however, suggest that the subcortical oculomotor centers or their afferent pathways are involved as well. Histopathologic studies have shown that the brain stem may also be damaged by cellular infiltration and hemorrhages.[27]

The total ophthalmologic morbidity was 60% (19 of 32 patients) if misalignment of the eyes was included as a criterion. Excluding misalignment, the average incidence of ocular morbidity was 40% (13 of 32 patients) in all patients examined: four of five children had the disseminated form (80%), two of five children had the skin, eye, and mouth disease (40%), and 14 of 22 children had the central nervous system form of the disease (32%). Mildly afflicted children had normal vision, unless corneal scars were present. Vision was severely impaired in children with grave neurologic sequelae, because of lesions in the brain, including the optic nerves, where transsynaptic degeneration of the visual pathway may occur. Cataracts are rare and more a sign of previous uveitis than a primary herpes simplex virus lesion within the lens. Necrotizing retinitis seems to be rare, but because it causes blindness, every attempt to recognize and treat this condition must be advocated. Special attention must be paid to the peripheral fundus because subclinical retinopathies with typical coarse hyperpigmentation were more common than previously described and did not resemble the lesions caused by other neonatally acquired infections, such as cytomegalovirus retinitis, toxoplasmosis, and so-called benign hyperpigmentations. These asymptomatic chorioretinal lesions may indicate a continued presence of herpes simplex virus in the retina and may cause the acute retinal necrosis syndrome later in life. Ophthalmologic long-term follow-up is as imperative as the prompt recognition and treatment of patients with neonatal herpes simplex disease.

References

1. Whitley, R. J., Nahmias, A. J., Visintine, A. M., Fleming, C. L., and Alford, C. A.: The natural history of herpes simplex virus infection of mother and newborn. Pediatrics 4:489, 1980.
2. Sullivan-Bolyai, J. Z., Hull, H. F., Wilson, C., Smith, A. L., and Corey, L.: Presentation of neonatal herpes simplex virus infections. Implications for a change in therapeutic strategy. Pediatr. Infect. Dis. 5:309, 1986.
3. Nahmias, A. J., Keyserling, H., and Kerrick, G. M.: In Remington, J., and Klein, J. (eds.): Infectious Disease of the Fetus and Newborn Infant. Philadelphia, W. B. Saunders, 1983, pp. 636–678.
4. Whitley, R. J., Nahmias, A. J., Soong, S. J., Galasso, G., Fleming, C., and Alford, C. A.: Vidarabine therapy of neonatal herpes simplex virus infections. Pediatrics 66:495, 1980.
5. Nahmias, A. J., Visintine, A. M., Caldwell, D. R., and Wilson, L. A.: Eye infections with herpes simplex viruses in neonates. Surv. Ophthalmol. 21:100, 1976.
6. Corey, L., Stone, E. F., Whitley, R. J., and Mohan, K.: Difference between herpes simplex virus type 1 and 2 neonatal encephalitis in neurological outcome. Lancet 2:1, 1988.
7. Tarkkanen, A., and Laatikainen, L.: Late ocular manifestations in neonatal herpes simplex infection. Br. J. Ophthalmol. 61:608, 1977.
8. Malm, G., Forsgren, M., el Azazi, M., and Persson, A.: Late nervous disturbances induced by neonatal herpes simplex virus infections. A follow-up study with special regard to neurological and behavioural changes. Acta Pediatr. Scand. In press.
9. Hagler, W. S., Walters, P. V., and Nahmias, A. J.: Ocular involvement in neonatal herpes simplex virus infection. Arch. Ophthalmol. 82:169, 1969.
10. Nahmias, A. J., and Hagler, W. S.: Ocular manifestations of herpes simplex in the newborn. Int. Ophthalmol. Clin. 12:191, 1972.
11. Yen, S. S C., Reagan, J. W., and Rosenthal, M. S.: Herpes simplex infection in the female genital tract. Obstet. Gynecol. 25:497, 1965.
12. Cibis, A., and Burde, R. M.: Herpes simplex virus-induced congenital cataracts. Arch. Ophthalmol. 85:220, 1971.
13. Bahrani, M., Boxerbaum, B., Gilger, A. P., Rosenthal, M. S., and Teree, T. M.: Generalized herpes simplex and hypoadrenocorticism. Am. J. Dis. Child. 111:437, 1966.
14. Florman, A. L., and Mindlin, R. L.: Generalized herpes simplex in an eleven-day-old premature infant. Am. J. Dis. Child. 83:481, 1952.
15. Mitchell, J. E., and McCall, F. C.: Transplacental infection by herpes simplex virus. Am. J. Dis. Child. 106:207, 1963.
16. Pettay, O., Leinikki, P., Donner, M., and Lapinleimu, K.: Herpes simplex virus infection in the newborn. Arch. Dis. Child. 47:97, 1972.
17. Cibis, G. W.: Neonatal herpes simplex retinitis. Albrecht v. Graefes Arch. Klin. Exp. Ophthalmol. 1961:39, 1975.
18. Reersted, P., and Hansen, B.: Chorio-retinitis of the newborn with herpes simplex virus type 1. Acta Ophthalmol. 57:1096, 1979.
19. Cogan, D. G., Kuwabara, T., Young, G. F., and

Knox, D. L.: Herpes simplex retinopathy in an infant. Arch. Ophthalmol. 72:641, 1964.
20. Golden, B., Bell, W. E., and McKee, A. P.: Disseminated herpes simplex with encephalitis in a neonate. JAMA 209:1219, 1969.
21. Mousel, D. K., and Missall, S. R.: Panuveitis and retinitis in neonatal herpes simplex infection. J. Pediatr. Ophthalmol. Strabismus 16:7, 1979.
22. Honda, Y., Nakazawa, Y., and Chihara, E.: Necrotizing chorioretinitis induced by herpes simplex virus infection in the neonate. Metab. Pediatr. Syst. Ophthalmol. 7:147, 1983.
23. Olson, R. M., Holland, G. N., Goss, S. J., Bowers, W. D., and Meyers-Elliott, R. H.: Routes of viral spread in the von Szily model of herpes simplex virus retinopathy. Curr. Eye Res. 6:59, 1987.
24. Miller, N. R.: Walsh and Hoyt's Clinical Neuroophthalmology, ed. 4., vol. I. Baltimore, Williams & Wilkins, 1982, pp. 330, 8, 329.
25. Kristensson, K., Suennerholm, B., and Lycke E.: Herpes simplex virus induced demyelination. J. Neurol. Sci. 60:247, 1983.
26. Sugimoto, T., Woo, M., Okazaki, H., Nishida, N., Hara, T., Yasuhara, A., Kasahara, M., and Kobayashi, Y.: Computed tomography in young children with herpes simplex virus encephalitis. Pediatr. Radiol. 15:372, 1985.
27. Young, G. F., Knox, D. L., and Dodge, P. R.: Necrotizing encephalitis and chorioretinitis in a young infant. Arch. Neurol. 13:15, 1964.

Ophthalmic miniature

I was completely absorbed by Lenin's personality. His powers of concentration were tremendous. When he talked to you, he made you feel you were the most important person in his life. He had a way of holding his face close to yours, his left eye squinting, but his right eye transfixing you as if it were trying to pierce your innermost soul. By the time we were through, I felt embraced, enveloped, as if I could trust him completely.

He began by giving me a quick glance sideways, as if to probe me with those sharp brown eyes. There seemed to be a trace of laughter in them.

Armand Hammer with Neil Lyndon, *Hammer: Witness to History*
London, Hodder and Stoughton, 1987, p. 141

Comparative Laboratory Diagnosis of Experimental Herpes Simplex Keratitis

Steven F. Lee, M.D., Gregory A. Storch, M.D., Charles A. Reed, M.S., Colleen M. Hagerty, B.S., and Jay S. Pepose, M.D.

We compared two commercially available tests, a direct immunofluorescence assay and an enzyme-linked immunosorbent assay (ELISA), to viral isolation in tissue culture for the laboratory diagnosis of untreated and partially treated experimental herpes simplex virus keratitis. New Zealand albino rabbits were inoculated bilaterally with herpes simplex virus-1 McKrae strain after corneal scarification. One eye of each rabbit was treated with a 1% trifluorothymidine solution daily, starting on the third day after inoculation. The direct immunofluorescence assay showed lower sensitivity for herpes simplex virus detection than viral isolation in tissue culture for both untreated and partially treated eyes. The Herpchek ELISA demonstrated similar sensitivity to tissue culture in detecting herpes simplex virus in untreated eyes. In the treated group, however, the Herpchek ELISA showed a higher percentage of eyes positive for herpes simplex virus than did viral isolation in tissue culture. After the initiation of antiviral therapy, eyes that no longer harbor infectious virus that can be isolated in tissue culture may remain herpes simplex virus antigen-positive and thus be more amenable to laboratory diagnosis using the rapid ELISA method.

Accepted for publication Oct. 3, 1989.

From the Departments of Ophthalmology (Drs. Lee and Pepose), Pediatrics (Dr. Storch, Mr. Reed, and Ms. Hagerty), and Pathology (Dr. Pepose), Washington University School of Medicine, St. Louis, Missouri. This study was supported in part by an unrestricted grant from Research to Prevent Blindness, Inc. (Dr. Pepose). Dr. Pepose is the recipient of the American College of Surgeons Faculty Fellowship. Dr. Lee is the recipient of a National Institutes of Health Vision Science Training Grant (EY07057).

Reprint requests to Jay Pepose, M.D., Department of Ophthalmology, Box 8096, Washington University School of Medicine, 660 S. Euclid Ave., St. Louis, MO 63110.

IN THE CLINICAL SETTING and particularly in referral-based practices, the diagnosis of atypical or partially treated cases of herpetic keratitis may be enigmatic. Incorrect diagnosis can lead to the inappropriate use of corticosteroids, with exacerbation of herpetic disease.[1,2] We evaluated and compared a direct immunofluorescence assay, an enzyme-linked immunoassay (Herpchek), and viral isolation in tissue for the laboratory diagnosis of untreated and partially treated experimental herpes simplex virus keratitis.

Material and Methods

The McKrae strain of herpes simplex virus type 1 was used. Virus stocks were prepared and titered on Vero cells using standard techniques.

New Zealand female albino rabbits weighing 2.0 to 3.0 kg were inoculated with herpes simplex virus-1 McKrae strain in minimal essential media (MEM) (1 to 10 × 104 PFU [plaque-forming units]/20 μl). A 20-μl drop of virus suspension was applied to each eye after corneal scarification with sterile No. 10 Barde-Parker scalpel blade in an interlocking crosshatch pattern. After viral inoculation, the eyes were closed and gently massaged for ten to 20 seconds. Rabbit eyes were stained with fluorescein and examined with a slit-lamp biomicroscope before inoculation and on postinoculation days 1, 3, 5, 7, 9, and 11.

Rabbits were treated with a 1% trifluorothymidine solution, which contains acetic acid, sodium acetate, sodium chloride, and thimerosal 0.001%. Treatment was started immediately after corneal swabbing on the third day after inoculation and continued for eight consecutive days. At two-hour intervals, one drop of the drug was applied uniocularly five times a day.

Each cornea was simultaneously swabbed with a sterile Dacron (Spectrum Laboratories) and Herptran swab (DuPont). The swabs, held adjacent to each other, were brushed lightly

across the cornea. The Dacron swabs were rolled over one well of a three-well slide for immunofluorescent staining.[3] The specimen on the slide was air-dried and fixed in acetone at −20 C for ten minutes. Slides were stored at −70 C. The Dacron swabs were then placed immediately in viral transport medium. Primary rabbit kidney cell monolayer tube cultures were inoculated with 0.3 ml of inoculated viral transport medium. The cells were incubated at 37 C and examined daily for seven days for the appearance of cytopathic effect characteristic of herpes simplex virus-1. The Herptran swabs were placed in Herptran medium and stored at −20 C. The specimens were then processed by the Herpchek assay.

The DuPont Herpchek direct herpes simplex virus antigen test has been described previously.[4] In brief, the four-hour assay is a forward sandwich enzyme immunoassay that utilizes purified rabbit polyclonal anti–herpes simplex virus antibodies for the capture of the herpes simplex virus antigen (Fig. 1). The capture antibody has been immobilized onto the interior surface of microtiter plate wells. One hundred microliters of the specimen in Herptran medium is incubated in the coated plate well to allow the binding of any herpes simplex virus antigen onto the solid phase. The immobilized antigen is then reacted with a second reagent (a mixture of biotinylated mouse monoclonal antibodies against herpes simplex virus). The amount of biotinylated antibody bound to the antigen is measured by binding with streptavidin-horseradish peroxidase conjugate, which catalyzes the conversion of a chromogenic substrate (o-phenylenediamine) into a colored product. The colored reaction product is detected by a dual spectrophotometric microtiter plate reader and indicates the presence of herpes simplex virus antigen in the sample.

Each well was read at 492 ± 2 nm with a 620-nm reference filter within 30 ± 5 minutes after addition of the stop solution. The negative control mean was calculated by averaging three negative control values. The positive cutoff value was determined by taking the negative control mean and adding to it a correction factor of 0.09. Samples with both duplicate absorbance values less than the cutoff value were considered negative for herpes simplex virus antigen. Samples with both duplicate values equal to or above the calculated cutoff value were considered positive for herpes simplex virus antigen. If one of the duplicate specimens was equal to or greater than the cutoff value while the other was below the cutoff value, then that specimen was retested in duplicate. If a similar result was obtained on repeat testing, then the final result was reported as indeterminate.

Specimen slides were removed from from storage at −70 C, thawed, and incubated for 30 minutes at 36 C with Syva types I and II (MicroTrak, Syva, Palo Alto, California), which

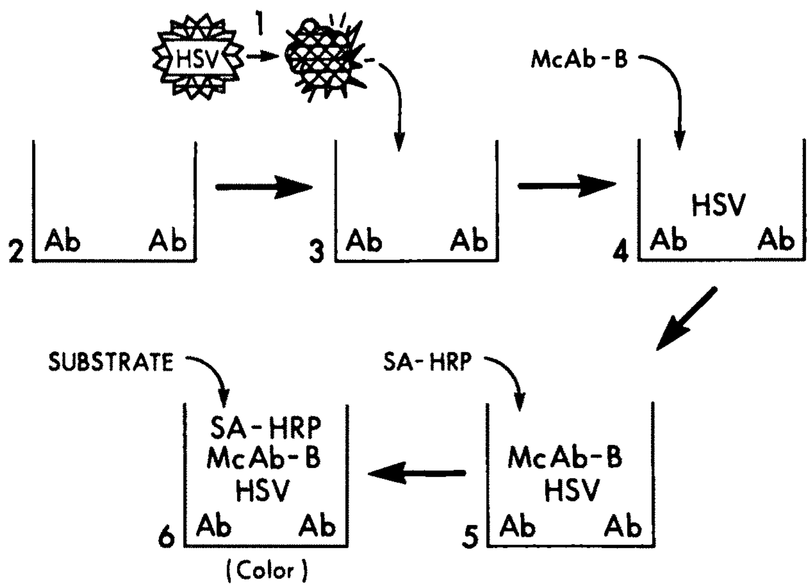


Fig. 1 (Lee and associates). (1) Swabs are placed in Herptran medium, which disrupts the viral envelope. (2) Microtiter plate-wells are coated with a polyclonal rabbit antibody against herpes simplex virus type 1 and 2 antigens. (3) The specimen is added to the coated wells, and the herpes simplex virus antigens are bound by the rabbit antibody. (4) Biotin-labeled monoclonal antibodies (Mc Ab-B) are added, which bind to the herpes simplex virus antigens. (5) A streptavidin-horseradish peroxidase conjugate is added, which binds to the biotin moiety on the monoclonal antibody. (6) The substrate, orthophenylenediamine (OPD), is added, together with hydrogen peroxide. Oxidation of the substrate results in a colorimetric reaction. (HSV indicates herpes simplex virus.)

contain fluorescein-labeled monoclonal antibodies against herpes simplex virus-1 and herpes simplex virus-2. Slides were then washed in phosphate-buffered saline for five minutes at room temperature. Samples were stained with 0.025% Evans blue in phosphate-buffered saline for five minutes at room temperature. Slides were rinsed in distilled water and air-dried, and mounting fluid and cover slips were added. The slides were read on the day of staining with an epifluorescent microscope. Direct specimens were considered adequate if at least 25 cells were seen, and specimens with fewer than 25 cells were reported as indeterminate. A positive specimen contained at least one cell with bright green granular staining.

Results

Untreated rabbits infected with the McKrae strain of herpes simplex virus-1 were examined daily by biomicroscopy for 12 days. All corneas showed signs of acute herpes simplex virus infection on days 3 and 5. Most corneas had classic dendrites, and the remaining corneas had other forms of ulcerative epithelial disease. Most of these epithelial lesions had resolved by day 9 or 11.

Thirty-two rabbit eyes were swabbed for analysis by direct immunofluorescence, the Herpchek ELISA, and tissue culture before inoculation and on the first and third days after inoculation. After the third day, one half of the eyes were placed in the treated group, and the rest were untreated. The attrition rate of rabbits because of encephalitis was zero before day 7, and two of 32 (6%) and six of 30 (20%) on days 9 and 11, respectively. The results of all three assays on untreated eyes are shown in Figure 2.

Direct immunofluorescence detected fewer untreated infected eyes than did the Herpchek ELISA or viral isolation in tissue culture. One day after inoculation, direct immunofluorescence gave positive results for six (19%) of 32 infected eyes. Peak detection occurred on days 3, 5, and 7 when 26 (81%) of 32, and 12 (75%) and 13 (81%) of 16 infected eyes were reported as giving positive results. Viral detection had dropped to five of 15 (33%) eyes and two of 12 (17%) eyes by days 9 and 11, respectively. Indeterminate results were included in the total number of eyes when calculating the percentage of positive results. Indeterminate samples constituted six (19%), two (6%), and one (3%) of 32 eyes before inoculation, postinoculation day 1, and postinoculation day 3, respectively. There were no indeterminate results by direct immunofluorescence after postinoculation day 3.

The Herpchek ELISA and viral isolation in tissue culture gave similar results in untreated eyes. On day 1, the Herpchek assay and tissue culture detected 12 (38%) and 18 (56%) of 32 infected eyes, respectively. Both assays showed peak detection, 32 (100%) of 32 eyes and 16 (100%) of 16 eyes on days 3 and 5, respectively. Similarly, the number of eyes giving positive results dropped to between two (17%) and three (25%) of 12 by both assays by day 11. There was one indeterminate result by the Herpchek assay during the entire study. This occurred on postinoculation day 1 and constituted one (3%) of 32 eyes. No animals that were scarified but

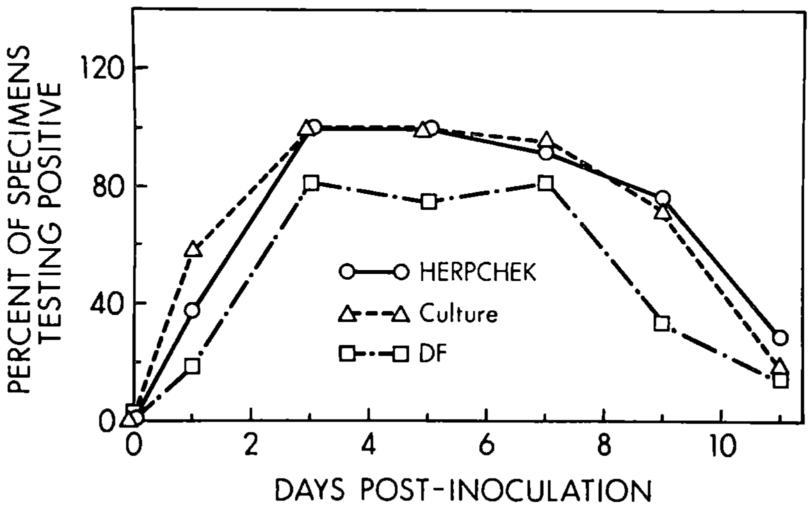


Fig. 2 (Lee and associates). Comparison of Herpchek, viral isolation in tissue culture, and direct immunofluorescence (DF) in detecting herpes simplex virus in untreated experimental herpes simplex virus keratitis.

not inoculated with herpes simplex virus tested positive by direct immunofluorescence, the Herpchek assay, or tissue culture at any time point.

Rabbits infected with herpes simplex virus and treated with trifluorothymidine were examined by slit-lamp biomicroscopy. On days 3 and 5, each cornea had classic dendrites or other forms of ulcerative epithelial disease. Most of these epithelial lesions had resolved by day 7 or 9, compared with day 9 or 11 in the untreated group.

Direct immunofluorescence showed a lower sensitivity to herpes simplex virus in treated eyes when compared to the Herpchek assay or viral isolation in tissue culture, as seen in Figure 3. On day 5, 48 hours after treatment, herpes simplex virus detection by direct immunofluorescence occurred in only nine (56%) of 16 eyes. On day 7, one (6%) of 16 treated eyes gave a positive result. On days 9 and 11, zero (0%) of 15 and one (8%) of 12 treated eyes gave positive results by direct immunofluorescence, respectively. There were no indeterminate results by direct immunofluorescence or the Herpchek assay after day 3.

The Herpchek assay demonstrated the highest sensitivity to herpes simplex virus after trifluorothymidine treatment. From days 5 to 11, there was a steady decrease from 15 of 16 (94%) to four of 12 (33%) eye specimens giving positive results. In contrast, viral recovery in tissue culture was 12 (75%) and three (19%) of 16, three (20%) of 15, and one (8%) of 12 treated eyes on days 5, 7, 9, and 11, respectively.

Discussion

We found in both treated and untreated groups of rabbits with herpes simplex keratitis that direct immunofluorescence had lower sensitivity in herpes simplex virus detection compared to the Herpchek assay or to viral isolation in tissue culture. In the untreated model, the Herpchek assay and tissue culture show similar sensitivities in detecting herpes simplex virus from corneal swabs. In the partially treated model, however, the Herpchek assay showed a higher percentage of eyes positive for herpes simplex virus than did viral isolation tissue culture.

Direct immunofluorescence is a rapid assay for the detection of herpes simplex virus from corneal swabs.[5,6] It is currently utilized in conjunction with viral isolation in tissue culture in many clinical laboratories. Several factors contribute to the lower sensitivity of direct immunofluorescence as compared to the Herpchek assay and tissue culture. One factor is the definition of a positive result. An insufficient number of total cells could cause a positive specimen to be read as indeterminate. Another factor is that the results rely on the subjective observations of a technician whose expertise may affect both the sensitivity and specificity of the assay. Finally, there is no amplification of the signal in this one-step process, as compared to other immunochemical assays, ELISA tests, or viral recovery in tissue culture.

In partially treated experimental herpes kera-

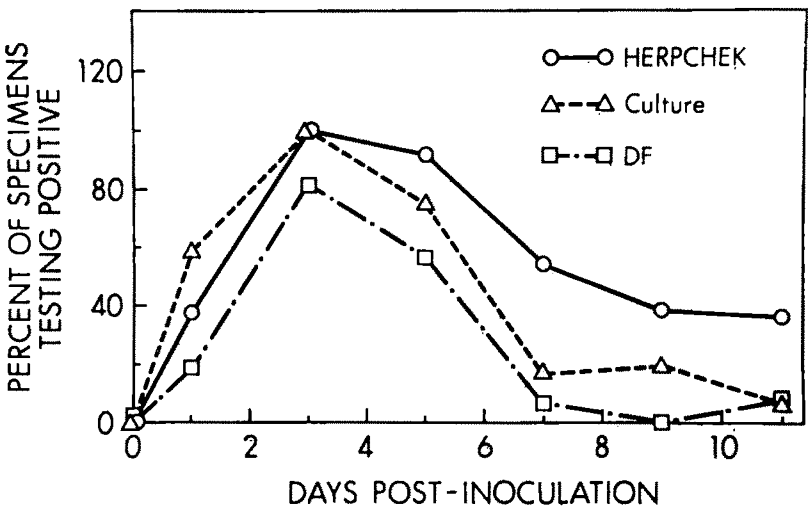


Fig. 3 (Lee and associates). Comparison of Herpchek, viral isolation in tissue culture, and direct immunofluorescence (DF) in detecting herpes simplex virus in partially treated experimental herpes simplex virus keratitis.

titis, the Herpchek assay showed a greater sensitivity than the conventional gold standard of viral isolation in tissue culture. This may be important in clinical practice when evaluating an atypical corneal lesion in a patient who has been partially treated with an antiviral medication. The enhanced detection capability of the Herpchek ELISA compared to tissue culture may reflect the latter's requirement for viable infectious particles that produce cytopathic effects in tissue culture, whereas the Herpchek assay detects viral antigens and amplifies its signal. Trifluorothymidine is a pyrimidine nucleoside that interferes with viral DNA synthesis. Unlike isolation in tissue culture, the Herpchek assay does not require the presence of infectious particles, such as virions, which may be absent in partially treated cases. As seen in our experimental model, partially treated eyes that give negative results for the herpes virus by tissue culture may still remain herpes simplex virus antigen-positive[4] and be more amenable to laboratory diagnosis using the Herpchek ELISA method.

References

1. Oh, J.: Enhancement of virus multiplication and interferon production by cortisone in ocular herpes virus infections. J. Immunol. 104:1359, 1970.

2. Thygeson, P., Hogan, M. J., and Kimura, S. J.: The unfavorable effect of topical steroid therapy on herpetic keratitis. Trans. Am. Ophthalmol. Soc. 58:245, 1960.

3. Duke, M. A., Webb, R. M., and Catalano, R. A.: A new rapid immunoperoxidase diagnostic staining of herpes simplex virus 1 indolent corneal ulcer. Cornea 3:115, 1984.

4. Pavan-Langston, D., and Dunkel, E. C.: A rapid clinical diagnostic test for herpes simplex infectious keratitis. Am. J. Ophthalmol. 107:675, 1989.

5. Kaufman, H. E.: The diagnosis of corneal herpes simplex infection by fluorescent antibody staining. Arch. Ophthalmol. 64:682, 1960.

6. Warford, A. L., Levy, R. A., and Rekrut, K. A.: Rapid laboratory diagnosis of herpes simplex virus. J. Med. Technol. 2:496, 1985.

OPHTHALMIC MINIATURE

Maigret sighed again. For a moment his eyes were vacant, while across his retina stretched a long strip of gleaming sand, beyond it a limitless glassy sea. . . .

Georges Simenon, *Maigret and the Fortuneteller*
Orlando, Florida, Harcourt Brace Jovanovich, 1989, p. 38

Orbital Myositis With Lyme Disease

Keith B. Seidenberg, B.A., and Martin L. Leib, M.D.

We examined, treated, and followed up for nine years a 5-year-old girl with active Lyme disease and orbital myositis. Clinically, the patient demonstrated typical symptoms for each of the major stages of Lyme disease, including fever, erythema chronicum migrans, aseptic meningitis, Bell's palsy, and arthritis. She subsequently developed clinical and computed tomographic evidence of orbital myositis. Although orbital myositis is generally considered to be an idiopathic inflammation, our findings suggest that in certain patients it may be a manifestation of Lyme disease.

Myositis secondary to Lyme disease has been reported to affect a growing number of muscles. A recent histopathologic study found evidence of the spirochete *Borrelia burgdorferi* in affected human skeletal muscle.[1] We examined, treated, and followed up for nine years a girl with active Lyme disease and associated orbital myositis.

Case Report

A 5-year-old girl from Westchester, New York, developed an erythematous enlarging rash, swelling of the left mastoid area, and a fever to 104 F in June 1980. After 36 hours on penicillin, her fever defervesced, and the rash resolved within one week. Three weeks later, the patient developed a left Bell's palsy. Tests at the time showed an increased erythrocyte sedimentation rate and a low-grade mononuclear cerebrospinal fluid pleocytosis. The Bell's palsy resolved without treatment within a month.

After remaining well for four months, the patient had a sudden onset of pain and swelling of the right knee. Knee x-rays, antinuclear antibody level, and rheumatoid factor were normal, and the patient had no further arthritic episodes.

Nine days before admission to Columbia's Babies Hospital, the patient experienced general malaise, erythema of the eyelid, orbital pain, proptosis in the right eye, and uncrossed diplopia. Four days before admission, she was treated at another hospital and a regimen of ampicillin, oxacillin, and topical chloramphenicol was started. She was transferred to Columbia-Presbyterian Medical Center on Dec. 24, 1980, without signs of improvement.

Physical examination disclosed a visual acuity of R.E.: 20/30 + 2 and L.E.: 20/25 − 2, a 30-prism diopter right esotropia, and a 14-prism diopter right hypotropia (Fig. 1). Limitation of right lateral rotation and of upward gaze of the right eye with increasing diplopia on right lateral gaze was noted. Saccadic velocity and other ocular motions appeared normal. A proptosis of 4 mm in the right eye was measured by Hertel exophthalmometry at a base of 77 mm. Cranial nerves V and VII were intact. The slit-lamp examination showed mild erythema of the eyelids, mild blepharoptosis, episcleral injection adjacent to the medial and inferior recti insertions, and normal corneas and anterior chambers. The pupils were briskly reactive, and there was no afferent pupillary defect. The complete blood cell count and results of thyroid function tests (T_4 and T_3) were normal, but the erythrocyte sedimentation rate was 50 mm/hr (Westergren). A computed tomographic scan disclosed proptosis, enlarged right medial and inferior recti muscles up to and including the insertions, possible optic nerve sheath involvement, normal sinuses, and haziness of the retrobulbar fat in the right eye (Fig. 2).

Accepted for publication Sept. 21, 1989.

From the Orbit and Plastics Service, Edward S. Harkness Eye Institute, Columbia-Presbyterian Medical Center (Dr. Leib), and the College of Physicians and Surgeons, Columbia University (Mr. Seidenberg and Dr. Leib).

Reprint requests to Martin L. Leib, M.D., Director, Orbit and Plastics Service, Edward S. Harkness Eye Institute, Columbia-Presbyterian Medical Center, 635 W. 165th St., New York, NY 10032.

Fig. 1 (Seidenberg and Leib). The patient with a right esotropia and hypotropia 12 hours after the intravenous administration of dexamethasone sodium phosphate.

Fig. 2 (Seidenberg and Leib). Axial computed tomography of orbits demonstrates proptosis, enlargement of the right medial rectus muscle up to and including the insertion, and haziness of the retrobulbar fat in the right eye.

A working diagnosis of Lyme disease complicated by orbital myositis in the right eye was made, and treatment was initiated with 10 mg of dexamethasone sodium phosphate intravenously. Within 24 hours, orbital swelling completely resolved, and the patient was started on 30 mg/day of oral prednisone and discharged several days later. On Jan. 16, 1981, the patient had a markedly increased IgM of 432 mg/dl.

The diplopia persisted after a 26-day regimen of 30 mg of prednisone daily. Examination showed visual acuity of 20/25 in both eyes, right esotropia of 45 prism diopters, no hypotropia, and almost full lateral excursion of the right eye. Other extraocular movements were full, and resolution of the episcleral injection was noted. The patient continued on tapering doses of prednisone, which were discontinued 11 weeks after admission. Four months after hospitalization, there was complete resolution of all ocular findings, including the diplopia. Follow-up has continued for nine years without recurring ocular problems.

Discussion

Before the appearance of orbital myositis, the patient had a classic case of Lyme disease. Epidemiologic risk was high because the child came from Westchester, New York, where a large number of deer ticks (*Ixodes dammini*) infected with the spirochete *Borrelia burgdorferi* exist during the summer. Clinically, the patient demonstrated typical symptoms from each of the three major stages of Lyme disease. Initially, she had a fever and a characteristic expanding rash, erythema chronicum migrans. The second stage is noted for the development of neurologic and cardiac disturbances. Although she did not demonstrate any cardiac involvement such as atrioventricular conduction blocks or myocarditis, she developed aseptic meningitis and cranial nerve palsy (Bell's palsy), which are two of the most common neurologic disturbances in Lyme disease, the third being peripheral radiculopathy. Finally, in the third stage, the patient developed arthritis, which most commonly affects the knees, but she did not develop chronic neurologic syndromes.[2]

Today, immunologic tests such as ELISA, specific for anti-*B. burgdorferi* titers, not available in the early 1980s, can be used to aid in the diagnosis of Lyme disease. Although useful, these serologic tests may give false-negative

results in the early stages of the disease or after early antibiotic treatment. Therefore, clinical signs such as erythema chronicum migrans and other organ involvement are also important criteria in diagnosing Lyme disease.[3,4]

Optimal treatment of Lyme disease in its different stages is being studied. Presently, a course of oral tetracycline or doxycycline for ten days to three weeks is advised for early disease. In addition to shortening the duration of the rash and flu-like symptoms, antibiotics are believed to reduce the patient's chances of developing the chronic illnesses of the later stages. Although all stages of Lyme disease respond to antibiotics, the results in later stages have been variable. Penicillin G and ceftriaxone are now being used for arthritis, carditis, and neurologic disturbances.[5]

Knowledge of ocular findings in Lyme disease is expanding. Although conjunctivitis is the most common symptom associated with the first stage of the disease, choroiditis, exudative retinal detachment,[6] iridocyclitis, retinal vasculitis, and optic perineuritis with macular edema,[7] and pseudotumor cerebri with disk edema have been other early-stage manifestations.[8] *Borrelia burgdorferi* has been isolated in the vitreous in the second stage of the disease,[9] and patients in the final stage of the disease have had bilateral keratitis[10-12] and impaired vision or diplopia secondary to neurologic disorders.[13]

Orbital pseudotumor is an antiquated term that denotes an idiopathic inflammatory process in the orbital tissues. More recently, terms such as "idiopathic orbital inflammation" or "inflammatory pseudotumor" are being used.[14] Periorbital pain, proptosis, blepharoptosis, and chemosis of acute onset are common characteristic manifestations of pseudotumor. With the use of more advanced diagnostic techniques such as computed tomography, pseudotumor is being subdivided into orbital myositis, dacryoadenitis, perineuritis, scleritis, and lymphoid hyperplasia, based on the primary tissue involved.[15,16] These distinctions are useful because they refer to different inflammatory processes that vary both in clinical response to and mode of therapy.[15]

Orbital myositis can often be confirmed by computed tomography, thereby eliminating the necessity for biopsy.[17,18] Computed tomography typically shows an enlarged orbital muscle, up to and including the insertion, often with an extension of the inflammation into the retrobulbar fat, which has a characteristic haziness.[15] This type of pseudotumor is notable for limitation of movement of the involved muscles, unimpaired vision, and rapid and dramatic response to corticosteroid treatment.[19,20]

In our patient, the diagnosis of orbital cellulitis was unlikely because of the clinical manifestation, failure of the patient to respond to antibiotics, and the radiographic picture. Graves' orbitopathy was not likely because of the normal thyroid function test results, clinical course, and the involvement of the muscle insertion as seen on computed tomography. Several cases of sixth cranial nerve palsy with Lyme disease, producing an esotropia and weakness of abduction, have been reported.[21] Normal rapid saccades, however, were seen in our patient.

The case described herein offers evidence of a myositis of extraocular muscles with active Lyme disease. In the differential diagnosis of orbital myositis, Lyme disease should be considered.

ACKNOWLEDGMENT

Allen Steere, M.D., of Yale University, examined the patient and corroborated the diagnosis of Lyme disease.

References

1. Atlas, E., Novak, S. N., Duray, P. H., and Steere, A. C.: Lyme myositis. Muscle invasion by *Borrelia burgdorferi*. Ann. Intern. Med. 109:245, 1988.
2. Steere, A. C.: Lyme disease. In Braunwald, E., Isselbacher, K. J., Petersdorf, R. J., Wilson, J. D., Martin, J. B., and Fauci, A. S. (eds.): Harrison's Principles of Internal Medicine, ed. 11. New York, McGraw-Hill, 1987, pp. 657–659.
3. Wilkinson, H. W.: Immunodiagnostic tests for Lyme disease. Yale J. Biol. Med. 57:567, 1984.
4. Craft, J. E., Grodzicki, R. L., and Steere, A. C.: Antibody response in Lyme disease. Evaluation of diagnostic tests. J. Infect. Dis. 149:789, 1984.
5. Treatment of Lyme disease. Med. Lett. Drugs Ther. 31:57, 1989.
6. Bialasiewicz, A. A., Ruprecht, K. W., Naumann, G. O. H., and Blenk, H.: Bilateral diffuse choroiditis and exudative retinal detachments with evidence of Lyme disease. Am. J. Ophthalmol. 105:419, 1988.
7. Wu, G., Lincoff, H., Ellsworth, R. M., and Haik,

B. G.: Optic disc edema and Lyme disease. Ann. Ophthalmol. 18:252, 1986.
8. Jacobson, D. M., and Frens, D. B.: Pseudotumor cerebri syndrome associated with Lyme disease. Am. J. Ophthalmol. 107:81, 1989.
9. Steere, A. C., Duray, P. H., Kauffman, D. J. H., and Wormser, G. P.: Unilateral blindness caused by infection with Lyme disease spirochete, *Borrelia burgdorferi*. Ann. Intern. Med. 90:382, 1985.
10. Orlin, S. E., and Lauffer, J. L.: Lyme disease keratitis. Am. J. Ophthalmol. 107:678, 1989.
11. Baum, J., Barza, M., Weinstein, P., Groden, J., and Aswad, M.: Bilateral keratitis as a manifestation of Lyme disease. Am. J. Ophthalmol. 105:75, 1988.
12. Kornmehl, E. W., Lesser, R. L., Jaros, P., Rocco, E., and Steere, A. C.: Bilateral keratitis in Lyme disease. Ophthalmology 96:1194, 1989.
13. Aaberg, T. M.: The expanding ophthalmologic spectrum of Lyme disease. Am. J. Ophthalmol. 107:77, 1989.
14. Spencer, W. H., Font, R. L., Green, W. R., Howes, E. L., Jakobiec, F. A., and Zimmerman, L. E.: Ophthalmic Pathology. An Atlas and Textbook, ed. 3. Philadelphia, W. B. Saunders, 1986, p. 2777.
15. Leib, M. L.: Computed tomography of the orbit. In Haik, B. G. (ed.): Advanced Imaging Techniques in Ophthalmology. Boston, Little Brown, 1986, pp. 103–121.
16. Lockie, P.: Acute orbital myositis. A case report. Aust. N.Z. J. Ophthalmol. 13:287, 1985.
17. Dresner, S. C., Rothfus, W. E., Slamovits, T. L., Kennerdell, J. S., and Curtin, H. D.: Computed tomography of orbital myositis. A.J.R. 143:671, 1984.
18. Rootman, J.: Diseases of the Orbit, ed 1. Philadelphia, J. B. Lippincott, 1988, pp. 159–175.
19. Hankey, G. J., Silbert, P. L., Edis, R. H., and Nicoll, A. M.: Orbital myositis. A study of six cases. Aust. N.Z. J. Med. 17:585, 1987.
20. Slavin, M. L., and Glaser, J. S.: Idiopathic orbital myositis. Report of six cases. Arch. Ophthalmol. 100:1261, 1982.
21. Pachner, A. R., and Steere, A. C.: The triad of neurologic manifestations of Lyme disease. Meningitis, cranial neuritis, and radiculoneuritis. Neurology 35:47, 1985.

OPHTHALMIC MINIATURE

When I looked up, MaryDell had closed her eyes, so that for a moment the full blue moons were eclipsed. I felt as if I were, in fact, staring at a dark, private side of her. Derek and I exchanged glances again, but of a different sort this time. Neither of us spoke. We waited for her.

When she opened her eyes, they were dulled, like her voice.

Nancy Pickard, *Dead Crazy*
New York, Simon and Schuster, Inc., 1988, p. 10

Granular Epithelial Keratopathy as an Unusual Manifestation of *Pseudomonas* Keratitis Associated With Extended-Wear Soft Contact Lenses

Steven I. Rosenfeld, M.D., Sid Mandelbaum, M.D., George F. Corrent, M.D., Stephen C. Pflugfelder, M.D., and William W. Culbertson, M.D.

We describe four patients who, using extended-wear soft contact lenses for myopia, abruptly developed ocular irritation and injection associated with elevated granular opacities initially confined to the central corneal epithelium. Cultures of the granular epithelial lesions were positive for *Pseudomonas aeruginosa* in all patients. Cultures of the contact lenses and lens case solutions grew *Pseudomonas* species and other gram-negative organisms. All patients responded to discontinuation of lens wear and frequent topical antibiotics. All recovered baseline visual acuity, and three have successfully resumed contact lens wear. These cases document that *Pseudomonas* keratitis may be manifested as a granular epithelial keratopathy.

MICROBIAL KERATITIS is the most serious complication of contact lens use.[1-7] Differentiating between infectious and sterile keratitis is often difficult clinically.[8,9] The initial laboratory evaluation and treatment varies depending on one's clinical impression about the nature of the keratitis. One should maintain a high level of suspicion for microbial keratitis in any contact lens–associated keratitis because of the potentially serious nature of the complication and the need to institute early and appropriate antimicrobial therapy.

We describe four patients who, using extended-wear soft contact lenses for myopia, developed a granular epithelial keratopathy that might have been mistaken for a sterile keratitis, but which proved to be culture-positive for *Pseudomonas aeruginosa*.

Accepted for publication Oct. 30, 1989.

From the Bascom Palmer Eye Institute, Department of Ophthalmology, University of Miami School of Medicine, Miami, Florida. Dr. Rosenfeld was a Heed Foundation Fellow (1984–1985).

Reprint requests to Steven I. Rosenfeld, M.D., Delray Eye Associates, 5210 Linton Blvd., Delray Beach, FL 33484.

Patients and Methods

We studied three patients seen at our institution and one patient seen in one of our (S.I.R.) private offices. All four patients were women with myopia who wore extended-wear soft contact lenses (Table 1).

Corneal cultures were obtained in a uniform fashion from all patients. After topical administration of proparacaine hydrochloride 0.5%, a sterile platinum spatula was used to obtain material from the areas of corneal lesions. The corneal scrapings were streaked on blood agar, chocolate agar, and Sabouraud's agar, and immersed in thioglycolate broth. In most cases, cultures of the conjunctiva, contact lens, and the lens case solutions were also obtained.

Patients were questioned on initial examination and at subsequent examinations about their contact-lens care regimens. Follow-up ranged from four to 36 months.

Case Reports

Case 1

A healthy 54-year-old woman with myopia had successfully worn extended-wear soft contact lenses for two years. She had a six-hour history of pain, redness, and photophobia of the left eye. She had last cleaned and sterilized her contact lenses five days previously. The right eye was normal. Visual acuity in the left eye was 20/40. There was mild left upper eyelid edema and conjunctival injection with a moder-

TABLE 1
CLINICAL DATA

PATIENT NO., AGE (YRS), SEX	LENGTH OF CONTACT LENS USE (MOS)	FREQUENCY AND METHOD OF CLEANING AND STERILIZATION	SALINE SOLUTION	AGE OF CONTACT LENSES (MOS)	VISUAL ACUITY	
					INITIAL EXAMINATION	FINAL
1, 54, F	24	Weekly, chemical	Preserved	13	20/40	20/25
2, 39, F	6	Weekly, chemical	Preserved	6	20/50	20/20
3, 32, F	12	Weekly, chemical	Nonpreserved	6	20/40	20/20
4, 25, F	4	Biweekly, heat	Nonpreserved (salt tablet)	2	20/50	20/20

ate follicular response (Table 1). There were approximately 20 coarse, elevated, granular lesions of the central corneal epithelium, without underlying stromal infiltrate (Figs. 1 and 2).

Cultures of several of the corneal epithelial lesions, the contact lens, the lens case solution, and the conjunctiva were obtained. The patient was treated with 3 mg/ml of gentamicin every two hours and bacitracin ointment every four hours. Forty-eight hours later, the epithelium had healed, but a fine cellular infiltrate of the anterior stroma had developed (Fig. 3). Dexamethasone phosphate 0.1% drops were added four times daily, and the antibiotics were continued. The corneal infiltrate resolved, and the cornea healed without scarring. All cultures grew *P. aeruginosa* with identical sensitivity profiles, except for the conjunctiva, which showed no growth. Additionally, *Pseudomonas maltophilia* and *Klebsiella pneumoniae* were isolated from the lens case solution (Table 2).

Case 2

A healthy 39-year-old woman with myopia had been wearing extended-wear soft contact lenses for six months. She had a 24-hour history of increasing pain, redness, and photophobia of her left eye. The right eye was normal. Left preauricular adenopathy was noted. The left eye demonstrated diffuse conjunctival injection with a mild follicular response, and multifocal, coarse, raised epithelial lesions in the central cornea without underlying stromal infiltrate (Table 1).

The patient was initially treated with scopolamine 0.25% drops every 12 hours. Twenty-four hours later, all but three of the coarse, punctate corneal lesions had resolved. Fine anterior stromal infiltrates had developed under these three remaining epithelial lesions.

Corneal and conjunctival cultures were obtained, and the patient was treated with 9 mg/ml of gentamicin and 50 mg/ml of cefazolin, alternately, every half hour. Prednisolone acetate 1% drops, four times a day, were added two days later, and the cornea healed with three small, para-axial anterior stromal scars. *Psuedomonas aeruginosa* was isolated from the corneal cultures, but no organisms grew from the conjunctival cultures (Table 2).

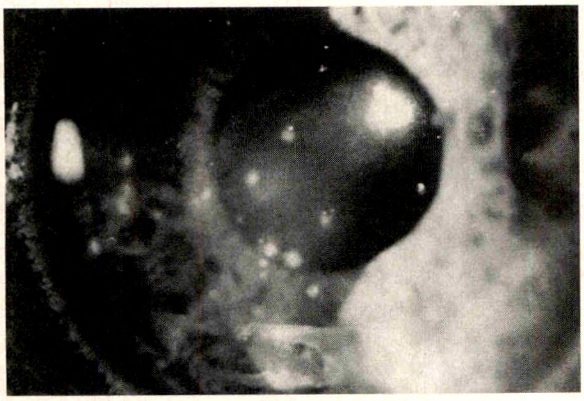


Fig. 1 (Rosenfeld and associates). Case 1. Multifocal, elevated, gray, granular lesions confined to central corneal epithelium.

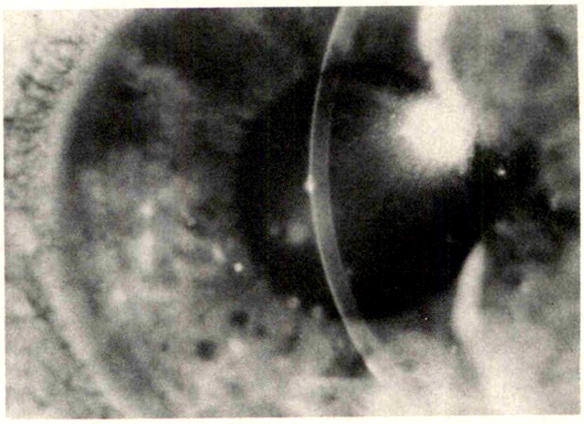


Fig. 2 (Rosenfeld and associates). Case 1. Slit beam demonstrating epithelial location and clear underlying stroma.

TABLE 1 *(Continued)*

FLUORESCEIN STAINING	STROMAL INFILTRATE: INITIAL EXAMINATION	STROMAL INFILTRATE: SUBSEQUENT	RESIDUAL SCARRING	RESUMED CONTACT LENS WEAR	TOTAL FOLLOW-UP (MOS)
Yes	No	Yes	No	No	22
Yes	No	Yes	Yes	Yes	20
Yes	No	Yes	No	Yes	36
Yes	No	Yes	Yes	Yes	4

Case 3

A pregnant 32-year-old woman with myopia had worn extended-wear soft contact lenses for one year without complications. She had a three-week history of reduced wearing time because of bilateral ocular irritation. The results of her ocular examination indicated that she had a dry eye syndrome related to pregnancy. She was allowed to continue extended-wear use of her contact lenses with the addition of topical nonthimerosol preserved lubricants.

The patient returned three days later with a 24-hour history of severe pain, redness, and photophobia of her left eye. Visual acuity had decreased to 20/40. There was mild conjunctival injection with a diffuse, fine papillary response. The central cornea contained numerous elevated, coarse, granular epithelial lesions within a zone of punctate epithelial erosions. The corneal stroma was clear (Table 1).

Cultures of the cornea, contact lens, and lens case solution were obtained. Treatment was begun with 3 mg/ml of tobramycin every two hours. Twenty-four hours later, stromal infiltrates had developed under the two remaining epithelial lesions. Dexamethasone phosphate 0.1% drops, four times a day, were added one week later. After two weeks, the patient's cornea was clear. All cultures grew *P. aeruginosa* with identical sensitivity profiles, and the lens case solution also grew *K. pneumoniae* and *Enterobacter cloacae* (Table 2).

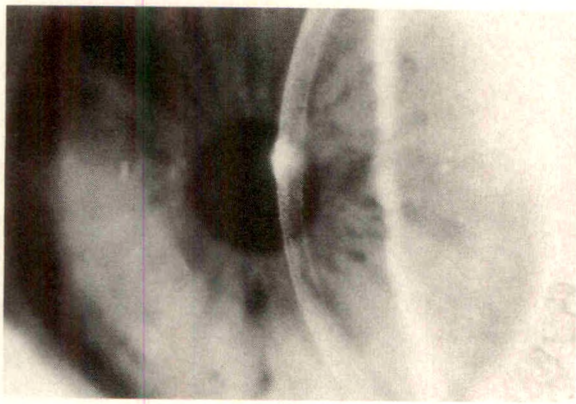


Fig. 3 (Rosenfeld and associates). Case 1. Slit beam demonstrating anterior stromal infiltrate beneath residual epithelial lesion after 24 hours of antibiotic treatment.

Case 4

A 25-year-old female nurse had worn extended-wear soft contact lenses successfully for four years. She had a two-day history of pain and redness in the left eye, which had not responded to self-prescribed gentamicin, 3 mg/ml, every 4 hours.

The right eye was normal. Visual acuity in the left eye was 20/50. There was moderate conjunctival injection with a follicular response, and mild chemosis. Five elevated, coarse, gray-white epithelial lesions were present in the central cornea, two of which stained with fluorescein. There were faint anterior stromal infiltrates underlying several of the lesions.

Because of her topical antibiotic use, no cultures were taken of the left eye. She was advised to discontinue the contact lenses in both eyes and use gentamicin drops, 3 mg/ml every three hours, and cyclopentolate 1% drops every six hours. When the patient returned 24 hours later, the condition of her left eye had not changed. She had not discontinued use of the extended-wear soft contact lens in her right eye, and her right eye now showed conjunctival injection with a follicular response and multiple central corneal epithelial lesions similar to those seen in her left eye (Fig. 4).

Cultures of the right cornea, conjunctiva, contact lens, and lens solution were obtained. She was treated with 9 mg/ml of tobramycin every half hour during the day, and every hour at night. Over the next 72 hours, the corneal epithelial lesions in both eyes decreased in size

TABLE 2
RESULTS OF BACTERIAL CULTURES

	PATIENT NO.			
SITE CULTURED	1	2	3	4
Cornea	*Pseudomonas aeruginosa*	*Pseudomonas aeruginosa*	*Pseudomonas aeruginosa*	*Pseudomonas aeruginosa*
Contact lens	*Pseudomonas aeruginosa*	*	*Pseudomonas aeruginosa*	*Pseudomonas aeruginosa*
Lens solution	*Pseudomonas aeruginosa*	*	*Pseudomonas aeruginosa*	*Pseudomonas aeruginosa*
	Pseudomonas maltophilia		*Enterobacter cloacae*	
	Klebsiella pneumoniae		*Klebsiella pneumoniae*	
Conjunctiva	No growth	No growth	*	Coagulase-negative staphylococci

*Indicates culture not obtained.

and number, but fine anterior stromal infiltrates developed under several of the lesions in the right eye. After one week, both corneas were quiet. All cultures, except for the conjunctiva, grew *P. aeruginosa* with identical sensitivity profiles (Table 2). Four months later, the right cornea showed faint anterior stromal scars.

Discussion

Bacterial keratitis is the most serious complication of extended-wear soft contact lenses.[1-7] Differentiating between infectious and noninfectious keratitis in patients wearing contact lenses can be difficult clinically.[8,9] Because microbial keratitis, particularly when caused by *Pseudomonas* species, can threaten vision and the structural integrity of the globe, it is critical to recognize these infections early to institute appropriate therapy.[10,11] We describe a manifestation of *Pseudomonas* keratitis that could easily be assumed to be noninfectious.

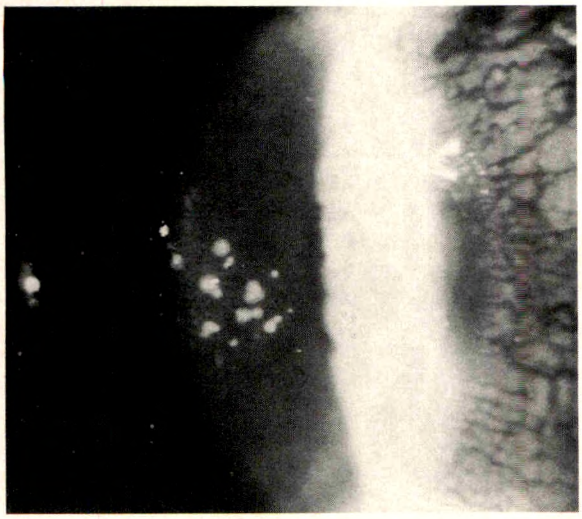


Fig. 4 (Rosenfeld and associates). Case 4. Similar multifocal granular corneal epithelial lesions.

There are multiple causes for punctate keratopathy associated with extended-wear soft contact lenses. Most of these are nonmicrobial in origin, and are thought to be caused by epithelial hypoxia, mechanical abrasion, or immunologic phenomena, including preservative hypersensitivity, reaction to lens deposits, or giant papillary conjunctivitis.[8,9,12-14] The epithelial erosions and occasional stromal infiltrates that characterize these entities are easily distinguished from the elevated granular lesions seen in our patients.

Biomicroscopically, the lesions in our patients were similar to those of superficial punctate keratitis described by Thygeson.[15] The clinical course of our patients was, however, different. Thygeson's superficial punctate keratitis, of unknown etiology, is usually found in uninflamed eyes, undergoes remissions and exacerbations, responds to topical corticosteroids, but not topical antibiotics, and may be symptomatically relieved by a soft contact lens.[15] Bacterial organisms have not been cultured from the epithelial lesions although there have been two reports of viral isolation that have not been confirmed.[16,17] In contrast, our patients developed symptoms of redness and irritation while wearing soft contact lenses, and *P. aeruginosa* grew from cultures of the lesions. The patients responded to topical antibiotics and did not develop recurrences with follow-up periods as long as 36 months.

These four cases of culture-positive *Pseudomonas* keratitis are unusual both in their manifestation and course. All patients had multifo-

cal, elevated, coarse, grayish lesions initially confined to the central corneal epithelium, many of which stained with fluorescein. All patients had moderate conjunctival injection but no visible anterior chamber inflammation. All patients developed anterior stromal infiltrates after the institution of antibiotic therapy. Although two eyes healed with residual anterior stromal scarring, all eyes recovered baseline visual acuity. These four cases demonstrated a less aggressive course than that considered typical for *Pseudomonas* keratitis.

Pseudomonas keratitis is usually characterized by a central or paracentral focus of epithelial ulceration, with dense stromal infiltrate and necrosis.[10] There is often an adherent, overlying mucopurulent discharge and a hypopyon.[10]

There are several possible explanations for the less aggressive course in these patients. *Pseudomonas* corneal ulcers may begin as an epithelial keratitis, and our patients may have been initially examined in this early stage. Institution of antibiotic therapy at this point probably modified the course of the disease process. The development of anterior stromal infiltrates underlying some of the lesions in all patients suggests the potential for progression to more typical suppurative ulceration if the eyes had not been treated with appropriate antibiotics. This situation may be a parallel to recent reports of contact lens wearers who had epithelial erosions that progressed to ulcerative *Pseudomonas* keratitis.[9]

These particular strains of *Pseudomonas* may have been relatively less virulent, possibly because of the lack of elaboration of destructive enzymes such as protease, elastase, lipase, exotoxin A, or other as yet undefined factors.[10,11] Using clinically obtained isolates, Bohigian and Escapini found differences in pathogenicity among different *Pseudomonas* strains tested on rabbit models.[18] Hazlett and associates have described a clinical isolate of *P. aeruginosa* that causes less virulent infections in humans and mice, despite producing the same toxin A, elastase, and general protease as the more virulent strains.[19] It is unlikely that host factors were significant, because our patients were all relatively young and healthy, as are most of the described patients with contact lens–associated microbial keratitis.[1-7]

We were unable to determine the precise cause of the granular epithelial lesions noted in these patients when they were initially examined. Because *P. aeruginosa* was cultured directly from the corneal lesions in all four patients, the lesions may represent epithelial cells damaged by *Pseudomonas* organisms. Alternatively, the granular epithelial changes may be an unusual manifestation of epithelial hypoxia, microscopic trauma, or a hypersensitivity response to the contact lens or lens solutions. *Pseudomonas* organisms may then have secondarily adhered to these granular lesions.

The latter hypothesis seems more likely, because animal models have demonstrated that corneal epithelial trauma is necessary to allow for *Pseudomonas* adherence to damaged epithelium or exposed stroma.[20-24] Adherence of bacteria to the epithelial surface is believed to be the necessary first step in the pathogenesis of *Pseudomonas* corneal ulceration.[20-24] The anterior stromal infiltrates that developed beneath some of the granular lesions in all patients, and the residual anterior stromal scarring in Patients 2 and 4, show the potential for progression to a more aggressive ulcerative form of keratitis.

Of the three lens care systems cultured, all were contaminated with *P. aeruginosa*, which had the same antibiotic sensitivity profile as the organisms cultured from the corneal lesions. The contaminated lens care systems are the probable source of infecting organisms in these cases. Because Donzis and associates[25] have reported that 50% of their asymptomatic contact lens patients had contaminated lens care systems, the potentially serious nature of lens care system contamination should not be underestimated.

The four cases reported herein document that *Pseudomonas* keratitis associated with extended-wear soft contact lenses may be manifested as a granular epithelial keratopathy. It is not clear whether this is a unique entity, or merely the earliest stages of what would eventually be typical ulcerative keratitis. Although similar granular epithelial lesions may occur other than in association with *Pseudomonas* organisms, the presence of this organism on the epithelial surface in the patients we describe argues for prompt initiation of antibiotic therapy directed at eradicating *Pseudomonas* species if these lesions are noted in a contact lens wearer. We recommend removing the lens, culturing the corneal lesions, and promptly instituting intensive topical fortified antibiotics with appropriate coverage for *P. aeruginosa*, pending culture results, in these patients. We would cautiously administer topical corticosteroids only if there is stromal inflammation that may result in scarring in the visual axis, and

only after control has been achieved of the bacterial organism that is present.

References

1. Wilson, L. A., Schlitzer, R. L., and Ahearn, D. G.: *Pseudomonas* corneal ulcers associated with soft contact-lens wear. Am. J. Ophthalmol. 92:546, 1981.
2. Adams, C. P., Cohen, E. J., Laibson, P. R., Galentine, P., and Arentsen, J. J.: Corneal ulcers in patients with cosmetic extended-wear contact lenses. Am. J. Ophthalmol. 96:705, 1983.
3. Lemp, M. A., Blackman, J., Wilson, L. A., and Leveille, A. S.: Gram-negative corneal ulcers in elderly aphakic eyes with extended-wear lenses. Ophthalmology 91:60, 1984.
4. Alfonso, E., Mandelbaum, S., Fox, M. J., and Forster, R. K.: Ulcerative keratitis associated with contact lens wear. Am. J. Ophthalmol. 101:429, 1986.
5. Ormerod, L. D., and Smith, R. E.: Contact lens-associated microbial keratitis. Arch. Ophthalmol. 104:79, 1986.
6. Mondino, B. J., Weissman, B. J., Farb, D., and Petit, T. H.: Corneal ulcers associated with daily-wear and extended-wear contact lenses. Am. J. Ophthalmol. 102:58, 1986.
7. Cohen, E. J., Laibson, P. R., Arentsen, J. J., and Clemons, C. S.: Corneal ulcers associated with cosmetic extended-wear soft contact lenses. Ophthalmology 94:109, 1987.
8. Stein, R. M., Clinch, T. E., Cohen, E. J., Genvert, G. I., Arentsen, J. J., and Laibson, P. R.: Infected vs sterile corneal infiltrates in contact lens wearers. Am. J. Ophthalmol. 105:632, 1988.
9. Udell, I. J., Ormerod, L. D., Bohiuk, V., and Abelson, M. B.: Treatment of contact lens-associated corneal erosions. Am. J. Ophthalmol. 104:306, 1987.
10. Hyndiuk, R. A., and Snyder, R. W.: Bacterial keratitis. In Smolin, G., and Thoft, R. A. (eds.): The Cornea. Scientific Foundations and Clinical Practice. Boston, Little, Brown, 1987, pp. 193–224.
11. Brown, S. I., Bloomfield, S. E., and Tam, W. I.: The cornea destroying enzyme of *Pseudomonas aeruginosa*. Invest. Ophthalmol. 13:174, 1974.
12. Jones, B. R.: The differential diagnosis of punctate keratitis. Trans. Ophthalmol. Soc. U.K. 80:665, 1960.
13. Binder, P. S.: Complications associated with extended-wear soft contact lenses. Ophthalmology 86:1093, 1979.
14. Mondino, B. J., and Groden, L. R.: Conjunctival hyperemia and corneal infiltrates with chemically disinfected soft contact lenses. Arch. Ophthalmol. 98:1767, 1980.
15. Thygeson, P.: Clinical and laboratory observations of superficial punctate keratitis. Am. J. Ophthalmol. 61:1344, 1966.
16. Braley, A. E., and Alexander, R. C.: Superficial punctate keratitis. Isolation of a virus. Arch. Ophthalmol. 50:147, 1953.
17. Lemp, M. A., Chambers, R. W., and Lundy, J.: Viral isolate in superficial punctate keratitis. Arch. Ophthalmol. 91:8, 1974.
18. Bohigian, G. M., and Escapini, H.: Corneal ulcer due to *Pseudomonas aeruginosa*. Arch. Ophthalmol. 85:405, 1971.
19. Hazlett, L. D., Zeit, R., Cramer, C., and Berk, R. S.: *Pseudomonas aeruginosa* induced ocular infections. A histological comparison of two bacterial strains of different virulence. Ophthalmic Res. 17:289, 1985.
20. Hyndiuk, R. A.: Experimental *Pseudomonas* keratitis. Trans. Am. Ophthalmol. Soc. 79:541, 1981.
21. Stern, G. A., Weitzenkorn, D., and Valenti, J.: Adherence of *Pseudomonas aeruginosa* to the mouse cornea. Epithelial v. stromal adherence. Arch. Ophthalmol. 100:1956, 1982.
22. Stern, G. A., Lubniewski, A., and Allen, C.: The interaction between *Pseudomonas aeruginosa* and the corneal epithelium. An electron microscopic study. Arch. Ophthalmol. 103:1221, 1985.
23. DiGaetano, M., Stern, G. A., and Zam, Z. S.: The pathogenesis of contact lens-associated *Pseudomonas aeruginosa* corneal ulceration. II. An animal model. Cornea 5:155, 1986.
24. Hyndiuk, R. A., Davis, S. D., Hatchell, D. L., Burd, E. M., Pederson, H. J., Divine, K. S., and Nassif, K. F.: Experimental *Pseudomonas* keratitis. Clinical and pathological observations. Cornea 2:103, 1983.
25. Donzis, P. B., Mondino, B. J., Weissman, B. A., and Bruckner, D. A.: Microbial contamination of contact lens care systems. Am. J. Ophthalmol. 104:325, 1987.

Traumatic Hyphema in an Urban Population

Thomas C. Spoor, M.D., Geoffrey M. Kwitko, M.D., John M. O'Grady, M.D., and John M. Ramocki, M.D.

We reviewed 241 patients (178 black and 63 white) who were examined and treated at the Detroit Medical Center between 1980 and 1989 for traumatic hyphema. Secondary hemorrhage occurred in 46 patients (19%) and was significantly higher in black patients ($P < .005$). Thirty-one patients (67%) developing secondary hemorrhage had an initial hyphema filling less than 25% of the anterior chamber. Patients treated with aminocaproic acid had secondary hemorrhages at a rate of 11% (six patients) compared to 21% (40 patients) in patients who were not treated with aminocaproic acid. The high risk of secondary hemorrhage with potential ocular damage in patients with traumatic hyphema, especially black patients, supports the benefit of hospitalization and the administration of aminocaproic acid.

SECONDARY HEMORRHAGE occurs in 2% to 38% of patients with traumatic hyphema and causes many of the serious ocular sequelae in these patients. Numerous studies have suggested possible regimens for decreasing the incidence of secondary hemorrhage, including strict bed rest,[1] topical cycloplegics,[2,3] patching of one or both eyes,[4] topical or systemic corticosteroids,[5] topical miotics,[2] hospitalization, and sedation.[6,7] The most appropriate regimen to prevent secondary hemorrhage remains uncertain. In randomized, double-masked clinical trials, aminocaproic acid appears to significantly decrease the incidence of secondary hemorrhage.[8-10] However, studies demonstrating a low incidence of secondary hemorrhage associated with traumatic hyphema,[11,12] as well as high cost and undesirable side effects, question the efficacy of routine administration of aminocaproic acid to all patients with traumatic hyphema.[13,14]

We analyzed records of patients with traumatic hyphema and evaluated the incidence of secondary hemorrhage in the predominantly black population of metropolitan Detroit served by the Detroit Medical Center. Additionally, we evaluated causes of traumatic hyphema, risk factors leading to secondary hemorrhage, and the role of aminocaproic acid in the prevention of secondary hemorrhage.

Subjects and Methods

The medical records of all patients examined and treated at the Detroit Medical Center between 1980 and 1989 with the diagnosis of traumatic hyphema were reviewed. All patients were hospitalized and treated with bed rest, patching, and sedation as necessary. A hyphema was considered to be present if either a layer of fresh blood or a clot was noted in the anterior chamber, or if diffuse erythrocytes were observed in the aqueous humor. Data collected on each patient included age, sex, race, sickle cell status, date of admission, length of hospital stay, cause of trauma, volume of initial hyphema, volume of secondary hemorrhage (if present), associated aspirin use, associated ocular and adnexal injuries, types of therapy, and complications. Secondary hemorrhage was defined as an increase in the volume of blood in the anterior chamber during the hospital stay. Patients excluded from this study included those with penetrating injuries to the globe or previous ocular surgery and those patients being treated for secondary hemorrhage.

Differences in race, age, and sex with respect to type of injury, incidence of secondary hyphema, and volume of initial hyphema were evaluated. All statistical analysis was done with the chi-square method. Two hundred forty-one patients with traumatic hyphema were treated at the Detroit Medical Center between 1980 and 1989. One hundred seventy-eight (74%) were

Accepted for publication Sept. 25, 1989.
From the Kresge Eye Institute, Wayne State University, Detroit, Michigan.

Reprint requests to Thomas C. Spoor, M.D., F.A.C.S., Kresge Eye Institute of Wayne State University, 3994 John R, Detroit, MI 48201

TABLE 1
CHARACTERISTICS OF PATIENTS WITH TRAUMATIC HYPHEMA (N = 241)

	NO.	%	RANGE	MEAN
Sex				
Male	189	78	—	—
Female	52	22	—	—
Race				
White	178	74	—	—
Black	63	26	—	—
Age	—	—	6 mos to 82 yrs	18.2 yrs

black, and 63 (26%) were white. One hundred eighty-nine (78%) were male, and 52 (22%) were female. Patients' ages ranged from 6 months to 52 years, with the mean 18.2 years (Table 1). Blows to the eye accounted for 147 (61%) of hyphemas, with projectile injuries occurring in 87 (36%). The remainder of hyphemas (six, or 3%) resulted from explosive injuries (Table 2).

Results

The causes of traumatic hyphema were markedly different in children and adults. Projectile injuries occurred in 73 of the 145 children (50%), with similar injuries occurring in 14 of the 96 adults (15%), which was statistically significant ($P < .005$). Blows to the eye, however, caused 68 of the 145 (47%) pediatric traumatic hyphemas, with similar injuries occurring in 80 of the 96 adults (83%), which was also a statistically significant difference ($P < .005$). The number of explosive injuries was similar for both children and adults. Sports-related injuries occurred in 22 patients (9%) and were equally distributed between children (14, or 10%) and adults (eight, or 8%).

Associated injuries to the eye and periocular structures occurred in 200 patients (83%). Only 41 patients (16%) had no associated injury. Associated injuries were diagnosed in nearly all parts of the eye and orbital tissues, with corneal abrasion most common (Table 3).

Secondary hemorrhage occurred in 46 patients (19%). There was a statistically significant difference ($P < .005$) in the rate of secondary hemorrhage when black patients (43, or 24%) were compared to white patients (three, or 5%) (Table 4). Males showed approximately the same

TABLE 2
CAUSES OF TRAUMATIC HYPHEMA

CAUSE	PATIENTS NO.	(%)
Projectile	87	(36.1)
Ball	22	(9.1)
Rock/dirt	20	(8.3)
BB	8	(3.3)
Woodchip	4	(1.7)
Bullet	4	(1.7)
Snowball	4	(1.7)
Slingshot	2	(0.8)
Shuttlecock	1	(0.4)
Hockey puck	1	(0.4)
Other	21	(8.7)
Blow	147	(61.0)
Fist/foot	39	(16.2)
Flexible object	29	(12.0)
Baseball bat	25	(10.4)
Fall	14	(5.8)
Dashboard	4	(1.7)
Other	36	(14.9)
Explosion	6	(2.4)
Firecrackers	3	(1.2)
Roll of caps	1	(0.4)
Battery	1	(0.4)
Hand grenade	1	(0.4)
Unknown	1	(0.4)
Total	241	(100)

TABLE 3
OCULAR AND PERIOCULAR INJURIES ASSOCIATED WITH TRAUMATIC HYPHEMA (N = 425)

SITE	INJURY	NO.	(%)
Orbit	Fracture	18	(7.5)
Cornea	Abrasion	63	(26.1)
	Blood stain	14	(5.8)
Globe	Secondary hemorrhage	46	(19.1)
	Pressure increase	21	(8.7)
Eyelid	Laceration	20	(8.3)
Lens	Cataract	9	(3.7)
	Subluxation	5	(2.1)
Angle	Recession	42	(17.4)
Iris	Mydriasis	30	(12.4)
	Dialysis	16	(6.6)
Vitreous	Hemorrhage	39	(16.2)
Retina	Macular edema	27	(11.2)
	Peripheral edema	25	(10.4)
	Retinal detachment	5	(2.1)
Optic nerve	Neuropathy	4	(1.7)
No associated injury	—	41	(17.0)

TABLE 4
SECONDARY HEMORRHAGE IN BLACK VS WHITE PATIENTS (P < .005)

	NO.	(%)	SECONDARY HEMORRHAGE	(%)
Black	178	(73.9)	43	(24.2)
White	63	(26.1)	3	(4.8)
Total	241	(100.0)	46	(19.1)

TABLE 5
SECONDARY HEMORRHAGE IN MALE VS FEMALE PATIENTS (P > .25)

	NO.	(%)	SECONDARY HEMORRHAGE	(%)
Males	189	(78.5)	38	(20.1)
Females	52	(21.5)	8	(15.4)
Total	241	(100.0)	46	(19.1)

rate of secondary hemorrhage (38, or 20%) compared to females (eight, or 15%) (Table 5), and children had a secondary hemorrhage rate (33, or 23%) similar to adults (13, or 14%) (Table 6). Most patients developing secondary hemorrhage (28, or 67%) had an initial hyphema filling less than 25% of the anterior chamber (Table 7). Sex, age, and cause of injury showed no statistically significant difference between patients with secondary hemorrhage and uncomplicated cases. Four patients had positive sickle cell trait, and none developed secondary hemorrhage.

All patients were admitted at the time of initial examination. In addition to bed rest, all patients were given topical cycloplegic agents as well as topical corticosteroids. The injured eye was patched and shielded in all patients. Of the 54 patients given aminocaproic acid, six (11%) suffered a secondary hemorrhage. Fifty two of these patients (96%) were black. Of the 187 patients not given aminocaproic acid, 40 (21%) had a secondary hemorrhage ($P < .1$).

The mean duration of hospital admission was 6½ days for those patients who had an uncomplicated course, which was significantly shorter than the mean duration for those patients with secondary hemorrhage (9.7 days).

Discussion

Previous studies have noted that traumatic hyphema is an injury of youth, with males at greater risk than females (Tables 5 and 6). Young males are traditionally more apt to engage in more violent activities. Of the patients in our study, 74% were black (Table 1), which approximates the racial distribution in the population of Detroit served by the Detroit Medical Center. The cause of injuries resulting in traumatic hyphema differed in this study compared to studies in other large metropolitan areas.[13,14] In this study, blows to the eye accounted for 61% of traumatic hyphemas, with projectile injuries causing only 36% of the cases (Table 2). The reverse is true in other studies.[13-18] Sports-related injuries occurred in 9% (22 patients), which is also different from previous studies.[12,19] As in other investigations, associated injuries accompanying traumatic hyphema were common and occurred in all parts of the eye and periocular tissues (Table 3).

Secondary hemorrhage has been reported to occur in 2% to 38% of traumatic hyphemas.[2,12] We report a frequency of 19% (46 patients). The black population demonstrated a significant increase in the rate of secondary hemorrhage ($P < .005$) compared to white patients (Table 4). Several studies show no racial difference in the rate of secondary hemorrhage.[8,20-22] Two other studies demonstrated a highly significant difference in rehemorrhage rates, with blacks being at higher risk than whites ($P < .05$).[23,24] Additionally, many traumatic hyphema studies have been

TABLE 6
SECONDARY HEMORRHAGE IN CHILDREN VS ADULTS (P > .05)

	NO.	(%)	SECONDARY HEMORRHAGE	(%)
Children	145	(60.2)	33	(22.8)
Adults	96	(39.8)	13	(13.5)
Total	241	(100.0)	46	(19.1)

TABLE 7
OCCURRENCE OF SECONDARY HEMORRHAGE BY VOLUME OF INITIAL HYPHEMA

VOLUME	NO.	(%)	CUMULATIVE %
Microscopic	3	(6.5)	6.5
>Microscopic to <25%	28	(60.9)	67.4
25% to 50%	10	(21.7)	89.1
50% to 75%	4	(8.7)	97.8
75% to 100%	1	(2.2)	100.0
Total	46	(100.0)	—

done in the predominantly white populations of Northern Europe, Canada, Australia, and Minnesota. These studies consistently show a rate of secondary hemorrhage under 10%.[12,19,25-32]

When the amount of blood in the anterior chamber is large at the time of initial diagnosis, secondary hemorrhage has been shown to occur more frequently ($P < .05$). In our study, however, 67% of secondary hemorrhages (28 patients) occurred when the initial hyphema filled less than 25% of the anterior chamber (Table 7). Previous studies have demonstrated no relationship between size of hyphema and incidence of secondary hemorrhage.[11,16-18] This phenomenon is difficult to explain because we tend to correlate more severe damage, and therefore a greater risk of secondary hemorrhage, with a larger hyphema. Our findings may reflect the higher risk of secondary hemorrhage in the more heavily pigmented eye.

All patients studied were treated similarly, with hospital admission, bed rest, sedation, topical cycloplegics, topical corticosteroids, and monocular patching used in all. The only difference in therapy was the use of aminocaproic acid in certain patients. Fifty-four patients were treated with aminocaproic acid, and six (11%) of these had a secondary hemorrhage. Fifty two of these patients (96%) were black. Of the remaining 187 patients not treated with aminocaproic acid, 40 (21%) had secondary hemorrhages. Our data agree with prospective randomized studies that have demonstrated a significant decrease in the rate of secondary hemorrhage in patients treated with aminocaproic acid.[8-10] These data may be more significant because most of our patients treated with aminocaproic acid were black, and they had a significantly lower incidence of secondary hemorrhage.

Those opposed to the routine use of aminocaproic acid call attention to its liabilities: cost of routine administration and side effects of nausea, vomiting, hypotension, diarrhea, and muscle cramps.[11,14] It is not clear whether aminocaproic acid should be considered for all hyphema patients; however, a trend seems to be emerging. With the documented increased risk of secondary hemorrhage in the black population, we believe that aminocaproic acid should routinely be administered to patients with traumatic hyphema. Additionally, because secondary hemorrhage accounts for many ocular complications associated with traumatic hyphema, aggressive treatment to prevent secondary hemorrhage is warranted. This includes hospital administration, bed rest, and sedation. Whether or not the risk/benefit ratio favors such aggressive therapy in the white population, which has a statistically lower risk of secondary hemorrhage, is left to the discretion of the physician.

References

1. Read, K., and Goldberg, M. F.: Comparison of medical treatment for traumatic hyphema. Trans. Am. Acad. Ophthalmol. Otolaryngol. 78:799, 1974.
2. Rakusin, W.: Traumatic hyphema. Am. J. Ophthalmol. 74:284, 1972.
3. Gilbert, H. D., and Jenson, A. D.: Atropine in the treatment of traumatic hyphema. Ann. Ophthalmol. 5:1297, 1973.
4. Edwards, W. C., and Layden, W. E.: Monocular versus binocular patching in traumatic hyphema. Am. J. Ophthalmol. 76:359, 1973.
5. Rynne, M. Y., and Romano, P. E.: Systemic corticosteroids in the treatment of traumatic hyphema. J. Pediatr. Ophthalmol. Strabismus 17:141, 1980.
6. Deutsch, T. A., and Goldberg, M. F.: Traumatic hyphema. Medical and surgical management. Clinical Modules for Ophthalmologists, Module 5. San Francisco, American Academy of Ophthalmology, 1984.
7. Wilson, F. M., II: Traumatic hyphema. Pathogenesis and management. Ophthalmology 87:910, 1980.
8. Crouch, E. R., Jr., and Frenkel, M.: Aminocaproic acid in the treatment of traumatic hyphema. Am. J. Ophthalmol. 81:355, 1976.
9. McCetrick, J. J., Jampol, R. M., Goldberg, M. F., Frenkel, M., and Fiscella, R. G.: Aminocaproic acid decreased secondary hemorrhage after traumatic hyphema. Arch. Ophthalmol. 101:1031, 1983.
10. Kutner, B., Fourman, S., Brein, K., Hobson, S., Mrvos, D., Sheppard, J., and Weisman, S.: Aminocaproic acid reduces the risk of secondary hyphema in patients with traumatic hyphema. Arch. Ophthalmol. 105:206, 1987.
11. Witteman, G. J., Brubaker, S. J., Johnson, M., and Marks, R. G.: The incidence of rebleeding in traumatic hyphema. Ann. Ophthalmol. 17:525, 1985.
12. Kraft, S. P., Christianson, M. D., Crawford, J. S., Wagman, R. D., and Antoszyk, J. H.: Traumatic hyphema in children. Treatment with epsilon-aminocaproic acid. Ophthalmology 94:1232, 1987.
13. Ophthalmology Journal Club: Aminocaproic acid. Arch. Ophthalmol. 102:818, 1984.
14. Kraft, S. P., and Crawford, J. S.: Traumatic hyphema therapy. Ophthalmology 95:709, 1988.
15. Thygeson, P., and Beard, C.: Observations on traumatic hyphema. Am. J. Ophthalmol. 35:977, 1952.
16. Spaeth, G. L., and Levy, P. M.: Traumatic hyphema. Its clinical characteristics and failure of estrogen to alter its course. A double-blind study. Am. J. Ophthalmol. 62:1098, 1966.
17. Edwards, W. C., and Layden, W. E.: Traumatic hyphema. A report of 184 consecutive cases. Am. J. Ophthalmol. 75:110, 1973.

18. Coles, W. H.: Traumatic hyphema. An analysis of 235 cases. South. Med. J. 61:813, 1968.
19. Kennedy, R. H., and Brubaker, R. F.: Traumatic hyphema in a defined population. Am. J. Ophthalmol. 106:123, 1988.
20. Thomas, M. A., Parrish, R. K., and Feuer, W. J.: Rebleeding after traumatic hyphema. Arch. Ophthalmol. 104:206, 1986.
21. Kushner, A. G.: Traumatic hyphema. Surv. Ophthalmol. 4:2, 1959.
22. Cole, J. G., and Byron, H. M.: Evaluation of 100 eyes with traumatic hyphema. Intravenous urea. Arch. Ophthalmol. 71:35, 1964.
23. Palmer, D. J., Goldberg, M. F., Frenkel, M., Fiscella, R., and Anderson, R. J.: A comparison of two dose regimens of epsilon aminocaproic acid in the prevention and management of secondary traumatic hyphemas. Ophthalmology 93:102, 1986.
24. Skalka, H. W.: Recurrent hemorrhage in traumatic hyphema. Ann. Ophthalmol. 10:1153, 1978.
25. Uusitalo, R. J., Saari, M. S., Aine, E., and Saari, K. M.: Tranexamic acid in the prevention of secondary hemorrhage after traumatic hyphema. Acta Ophthalmol. 59:539, 1981.
26. Agapitos, P. J., Noel, L. P., and Clarke, W. N.: Traumatic hyphema in children. Ophthalmology 94:1238, 1987.
27. Bramsen, T.: The influence of antifibrinolytica on traumatic hyphaema and corneal oedema. Acta Ophthalmol. 145(suppl.):1, 1980.
28. Öhrström, A.: Treatment of traumatic hyphaema with corticosteroids and mydriatics. Acta Ophthalmol. 50:549, 1972.
29. McDermott, N. D., and West, R. H.: Traumatic hyphaema. A general hospital experience. Med. J. Aust. 2:593, 1976.
30. Littlewood, K. R.: Blunt ocular trauma and hyphaema. Aust. J. Ophthalmol. 10:263, 1982.
31. Bedrossian, R. H.: The management of traumatic hyphema. Ann. Ophthalmol. 6:1016, 1974.
32. Varnek, L., Daisgaard, C., Hansen, A., and Klie, F.: The effect of tranexamic acid on secondary haemorrhage after traumatic hyphaema. Acta Ophthalmol. 58:787, 1980.

Ophthalmic miniature

There was something about Ned. For one thing, he seemed as smart as I *remembered* being. Which was, truth be told, and allowing for mistakes of recollection, pretty crack-outfit bright. On balloon tires as we rattled through Virginia—me holding our newest baby—I sat recalling how one morning when Ned had been nearbout a year old, his eyes were just starting to like the middle distance. His eyes'd finally settled into their true color.

Alan Gurganus, *Oldest Living Confederate Widow Tells All*
New York, Alfred A. Knopf, Inc., 1989, p. 324

Cyanoacrylate Tissue Adhesive in the Management of Recurrent Retinal Detachment Caused by Macular Hole

Sherif M. Sheta, M.D., Tetsuo Hida, M.D., and Brooks W. McCuen II, M.D.

Nine eyes of nine patients with rhegmatogenous retinal detachment caused by a macular hole were treated by the transvitreal application of cyanoacrylate tissue adhesive to the macular hole. Eight of the nine eyes had previously failed conventional vitreous surgery with gas tamponade and laser photocoagulation. Eight eyes (89%) were completely reattached with a minimum follow-up of three months. In the successfully treated eyes, postoperative visual acuity was 20/200 in two eyes, 20/400 to 5/200 in five eyes, and less than 5/200 in one eye. Direct sealing of macular holes in difficult cases may obviate the need for extended intraocular tamponade or macular buckling with their associated complications.

RECENT SURGICAL TECHNIQUES for the management of retinal detachment caused by macular holes include pneumatic retinopexy using air or gas and pars plana vitrectomy with fluid-air exchange sometimes followed by laser application around the edges of the macular hole.[1,2] These techniques are appealing because of their relative simplicity, effectiveness, and minimization of damage to the macular area. Unfortunately, they are not always successful, particularly in severely myopic eyes with posterior staphylomas and depigmented retinal pigment epithelium, for which laser photocoagulation is less effective in achieving a chorioretinal adhesion. The alternatives in such failed cases include a permanent silicone oil tamponade or scleral buckling of the macula.[3,4] Silicone oil is an effective long-lasting tamponade, but it is associated with significant postoperative complications.[5] Macular buckling is difficult and hazardous, especially in myopic eyes with posterior staphylomas, and macular diathermy causes irreversible damage to macular function.[6]

We have previously described experimental models of rhegmatogenous retinal detachment and repair during vitreous surgery utilizing transvitreal cyanoacrylate retinopexy.[7,8] Rapid and strong chorioretinal adhesions were obtained with cyanoacrylate retinopexy with minimal clinically detectable toxic effects observed in air-filled eyes.[9] Cyanoacrylate retinopexy has also been used successfully in selected eyes with complicated retinal detachment and proliferative vitreoretinopathy after failed primary vitreous surgery.[10] We evaluated the efficacy of the transvitreal application of cyanoacrylate tissue adhesive to achieve permanent closure of macular holes in cases of recurrent retinal detachment after failure of conventional vitrectomy techniques.

Subjects and Methods

Between November 1987 and December 1988, nine patients with retinal detachment caused by macular holes were treated. Eight of the nine patients were considered for cyanoacrylate retinopexy only after conventional retinal surgery, including encircling scleral buckle, vitrectomy, membrane peeling, intraocular gas tamponade, and laser photocoagulation to the edges of the macular hole were unsuccessful in reattaching the retina. In one patient, the indication was the inability to maintain adequate postoperative positioning because of old age and a recent myocardial infarction.

Accepted for publication Oct. 2, 1989.
From the Department of Ophthalmology, Cairo University, School of Medicine, Cairo, Egypt (Dr. Sheta); the Department of Ophthalmology, Kyorin University, School of Medicine, Tokyo, Japan (Dr. Hida); and the Department of Ophthalmology, Duke University Eye Center, Durham, North Carolina (Dr. McCuen). This study was funded in part by the Adler Foundation, New York. This study was presented at the Sixth Vail Vitreoretinal Seminar, Vail, Colorado, March 17, 1989.
Reprint requests to Sherif M. Sheta, M.D., 3, Hoda Shaarawi St., Bab El Louk, Cairo 11111, Egypt.

All eyes underwent a preoperative ocular examination, including visual acuity testing and measurement of intraocular pressure as well as slit-lamp, fundus contact lens, and binocular indirect ophthalmoscopic examinations. The degree and extent of proliferative vitreoretinopathy, if present, were graded according to the classification system proposed by the Retina Society Terminology Committee.[11] At each follow-up visit, corrected visual acuity testing, intraocular pressure measurement, slit-lamp examination, and binocular indirect ophthalmoscopy were performed.

The average age of the patients was 59 years (range, 51 to 69 years) and seven of the nine patients (78%) were female. Five eyes were either aphakic preoperatively or rendered aphakic during surgery. Proliferative vitreoretinopathy classified as grades C2 and C3 was identified in two eyes (22%). The period of follow-up ranged from three to 15 months (average, seven months). All patients showed retinal detachment with a macular hole and no other retinal breaks. All macular holes were idiopathic with no history of trauma, uveitis, or proliferative diabetic retinopathy. Eight eyes were myopic (average, 9 diopters), and the axial length of the eyes ranged from 25 to 32 mm. Eight of the nine patients had undergone at least two previous operations for the treatment of the macular hole detachment, including peripheral scleral buckling, vitrectomy, repeat fluid-gas exchange, and attempts at laser treatment to the macular hole.

During the reoperation with cyanoacrylate tissue adhesive, the vitrectomy was revised with removal of any condensed peripheral vitreous remnants that still remained. Concurrent conventional intracapsular lens removal was performed in two eyes in which posterior visualization was inadequate because of cataract. Bimanual dissection of epiretinal membranes using a fiberoptic light pic and microforceps was used in eyes with proliferative vitreoretinopathy.

The technique of tissue adhesive delivery to the macular hole was similar to that used in our experimental model.[7] Because aqueous fluid stimulates polymerization of cyanoacrylate, special care was taken to dry the retinal surface with repeated fluid aspiration, using a soft-tipped extrusion needle to prevent the tissue adhesive from hardening before reaching the chorioretinal interface. An equal mixture of n-butyl-2-cyanoacrylate (Histoacryl) and iophendylate (Pantopaque) was used to delay the polymerization time of the tissue adhesive to approximately two to five seconds. We used our previously described cyanoacrylate microinjector to deliver small amounts of glue to the macular hole.[7] The center of the macular hole was touched with the small bubble of cyanoacrylate. Contact of the tissue adhesive bubble with the chorioretinal interface broke the surface tension of the bubble and allowed the tissue adhesive to spread slowly and cover the edges of the hole. The entire hole was usually covered with one application of glue. In one patient, supplemental laser photocoagulation of the edges of the macular hole was performed postoperatively.

Results

Complete retinal reattachment was produced in eight of the nine patients (89%) (Fig. 1). In the successful cases, the macular holes remained sealed during the follow-up period (three to 15 months, average seven months). In one patient, the cyanoacrylate tissue adhesive was found detached from the macular hole on the first postoperative examination, and the retina redetached after absorption of the air tamponade. This patient refused further surgical intervention. Another eye developed a crescent-shaped retinal break at the edge of the glue one month after surgery. The retina remained attached, and laser application to the tear was performed to prevent recurrence of retinal detachment. The postoperative intraocular pressure was normal, with one exception in which an early transient increase of intraocular pressure occurred. The increase was successfully managed with a topical beta-blocker. No other complications were observed.

At the last follow-up examination, visual acuity had improved in the eight successfully treated eyes. Visual acuity was 20/200 in two patients, 5/200 or better in five patients, and less than 5/200 in one patient. Visual acuity less than 5/200 was caused by a late nuclear sclerotic lens change. Plotting of the central visual field was done in some patients with the Humphrey visual field analyzer. The size of the postoperative scotoma was comparable to that caused by laser treatment (Fig. 2).

Discussion

The current management of retinal detachment caused by idiopathic macular holes in-

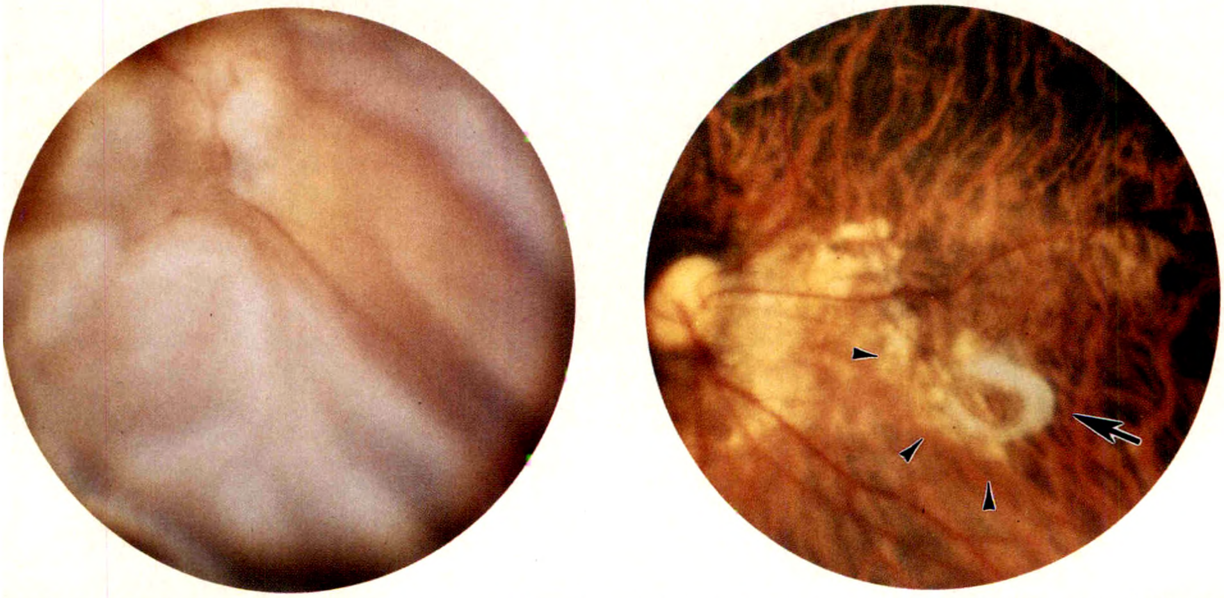


Fig. 1 (Sheta, Hida, and McCuen). Left, Fundus of the left eye of a patient after failed vitrectomy, fluid-gas exchange, and attempts at laser photocoagulation to the macular hole. Right, Fundus of the same patient after revision of vitrectomy, fluid-air exchange, and cyanoacrylate retinopexy of the macular hole. The glue appears as a whitish rim around the macular hole (arrow) with underlying previous laser marks (arrowhead).

volves a variety of surgical options. Outpatient pneumatic retinopexy using air or gas may succeed in reattaching some detachments with no visible vitreoretinal connections.[1] In 1982, Gonvers and Machemer[2] reported six cases of retinal detachment caused by macular holes treated successfully with vitrectomy followed by fluid-gas exchange without macular coagulation or buckling. When recurrence of the detachment occurs after repeated attempts at fluid-gas exchange and laser treatment in eyes with macular holes, silicone oil tamponade or macular buckling may be considered. Long-lasting intraocular tamponade with silicone oil is useful in maintaining retinal attachment, but it is not without complications.[5] Macular buckling is difficult and even hazardous in myopic eyes, especially in those with posterior staphylomas.[6] Additionally,

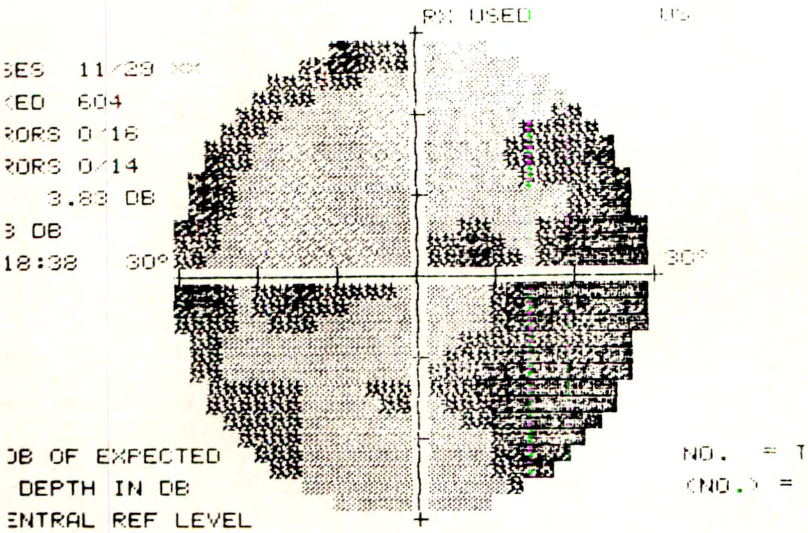


Fig. 2 (Sheta, Hida, and McCuen). Central field plotting for the same patient in Figure 1 showing a paracentral scotoma attributable to eccentric fixation.

macular function may also be further impaired by the distorting effect of macular buckles or by macular diathermy.

Cyanoacrylate retinopexy has significant theoretical advantages over retinopexy produced by cryotherapy, photocoagulation, or diathermy. We have shown in both the rabbit and the monkey that effective transvitreal cyanoacrylate retinopexy is technically possible in the treatment of experimental rhegmatogenous retinal detachment.[7,8] The chorioretinal adhesions produced by this technique occur quickly, are approximately twice as strong as the adhesions of transscleral retinal cryopexy, and are long lasting. By increasing the speed and strength of the chorioretinal adhesions, cyanoacrylate retinopexy might allow retinal breaks to remain closed when inadequate intraocular tamponade or residual or recurrent retinal traction would reopen thermally treated macular holes. Additionally, in the case of small macular holes in which the tissue adhesive covers the retinal defect, the glue may act as a patch that seals the break even if no chorioretinal adhesion were to be produced.

Most retinal detachments caused by macular holes occur in severely myopic eyes, which are frequently associated with posterior staphylomas. In these eyes, the macular hole is usually difficult to treat adequately because of associated atrophy of the retinal pigment epithelium and choroid. Laser-induced chorioretinal adhesions are not always possible, and retinal shortening and stretch may pull the retina loose after a temporary intraocular tamponade has disappeared. Cyanoacrylate retinopexy allows immediate closure of the hole without the need for laser photocoagulation or postoperative positioning. The strong adhesion produced by cyanoacrylate retinopexy also helps resist any unrelieved traction associated with the staphyloma or proliferative vitreoretinopathy or both.

Complications related to the use of cyanoacrylate were infrequent. In one eye, cyanoacrylate came loose from the retina by the first postoperative examination, and the retina redetached after disappearance of the tamponading air bubble. This patient was severely myopic with a large posterior staphyloma (axial length, 32 mm). Repeated attempts to dry the central retina during fluid-gas exchange failed to completely reattach the retina, which may have caused premature glue polymerization before it reached the chorioretinal interface. We are not sure why a late crescent-shaped tear developed adjacent to the cyanoacrylate site in one eye. This complication may be attributed to slow shrinkage of the glue after initial polymerization, or it may represent a localized toxic effect to the retina in the vicinity of the glue. A similar complication occurred experimentally when glue was applied through silicone oil.[12]

One limitation of cyanoacrylate retinopexy in air-filled eyes is the necessity for excellent visualization of the chorioretinal interface to apply a small amount of tissue adhesive safely and accurately. If lens opacification precludes perfect visualization, the lens should be sacrificed. In aphakic eyes, corneal striae may occur during fluid-gas exchange, significantly reducing visualization of the macular region. This can usually be managed by coating the endothelial surface of the cornea with sodium hyaluronate.[13] If visualization is still imperfect, glue application should be abandoned. Another difficulty in severely myopic eyes with posterior staphylomas and central chorioretinal atrophic changes is the accurate identification of the macular hole after flattening of the retina by fluid-gas exchange. In such situations, noting a landmark, such as a nearby vessel or a patch of underlying choroidal pigmentation, before fluid-gas exchange may help with the accurate glue application to the macular hole.

Despite our generally encouraging results in this study, we believe that cyanoacrylate retinopexy is best reserved for eyes that have failed conventional techniques of vitrectomy, repeated fluid-gas exchange, and laser photocoagulation, and that would otherwise be considered for macular buckling or permanent tamponade with silicone oil. Patients who are unable to cooperate with postoperative positioning may also be potential candidates for this approach.

References

1. Miyake, Y.: A simplified method of treating retinal detachment with macular hole. Long-term follow-up. Arch. Ophthalmol. 104:1234, 1986.

2. Gonvers, M., and Machemer, R.: A new approach to treating retinal detachment with macular hole. Am. J. Ophthalmol. 94:468, 1982.

3. Sheta, S. M., and Saad, A. A.: The use of silicone oil in advanced cases of proliferative vitreoretinopathy. Bull. Ophthalmol. Soc. Egypt 80:351, 1987.

4. Siam, A. L.: Management of central retinal detachment due to macular hole. Br. J. Ophthalmol. 57:351, 1973.

5. McCuen, B. W., II, de Juan, E., Landers, M. B., and Machemer, R.: Silicone oil in vitreoretinal surgery. Part 2. Results and complications. Retina 5:198, 1986.

6. Zayed, A., El-Gindi, F., Osman, L., and Sheta, S. M.: Vitrectomy for treatment of retinal detachment due to macular holes. Bull. Ophthalmol. Soc. Egypt 78:125, 1985.
7. McCuen, B. W., II, Hida, T., Sheta, S. M., Isbey, E. K., Hahn, D. K., and Hickingbotham, D.: Experimental transvitreal cyanoacrylate retinopexy. Am. J. Ophthalmol. 102:199, 1986.
8. Hida, T., Sheta, S. M., Proia, A. D., and McCuen, B. W., II: Experimental transvitreal cyanoacrylate retinopexy in a primate model. Am. J. Ophthalmol. 103:782, 1987.
9. Hida, T., Sheta, S. M., Proia, A. D., and McCuen, B. W., II: Retinal toxicity of cyanoacrylate tissue adhesive in the rabbit. Retina 8:148, 1988.
10. McCuen, B. W., II, Hida, T., and Sheta, S. M.: Transvitreal cyanoacrylate retinopexy in the management of complicated retinal detachment. Am. J. Ophthalmol. 104:127, 1987.
11. The Retina Society Terminology Committee: The classification of retinal detachment with proliferative vitreoretinopathy. Ophthalmology 90:121, 1983.
12. Sheta, S. M., Hida, T., and McCuen, B. W., II: Experimental transvitreal cyanoacrylate retinopexy through silicone oil. Am. J. Ophthalmol. 102:717, 1986.
13. Landers, M. B., III: Sodium hyaluronate (Healon) as an aid to internal fluid-gas exchange. Am. J. Ophthalmol. 94:557, 1982.

OPHTHALMIC MINIATURE

In 1981, Derek Briggs continued his dispersion of the bivalved arthropods into a series of orphaned groups (with *Canadaspis* holding increasingly lonely vigil as a true crustacean). Briggs used all twenty-nine specimens to decide the fate of *Odaraia*, the largest bivalved arthropod in the Burgess Shale (up to six inches long). At the front of its head, and extending beyond the carapace, *Odaraia* bears the largest eyes of any Burgess arthropod. Yet Briggs could find only one other structure on the head—a single pair of short ventral appendages behind the mouth. (This arrangement, with no antennae and only one post-oral pair of appendages, is unique, and would be sufficient in itself to mark *Odaraia* as an orphan among arthropods.)

Stephen J. Gould, *Wonderful Life, The Burgess Shale and the Nature of History*
New York, W. W. Norton, 1989, pp. 173–174

Factors Prognostic of Visual Outcome in Patients With Subretinal Hemorrhage

Steven R. Bennett, M.D., James C. Folk, M.D., Christopher F. Blodi, M.D., and Marie Klugman, Ph.D.

We reviewed the charts of 29 patients with large subretinal hemorrhages involving the center of the fovea to evaluate factors that might be prognostic of visual outcome. The average final visual acuity was 20/480 with a mean follow-up of three years. Patients with thick hemorrhages (causing an obvious elevation of the fovea) had worse final visual acuity than patients with thin hemorrhages ($P = .02$). The diameter of the hemorrhage was not a significant predictor of outcome. Patients with aging macular degeneration had poorer final visual acuity (mean, 20/1,700, $P = .002$), and patients with choroidal ruptures had better final visual acuity, (mean 20/35, $P < .001$) than the remainder of the patients. We found that the presence of aging macular degeneration was a more important predictor of the outcome of legal blindness than the thickness of the hemorrhage ($P = .03$). Although the prognosis in patients with subfoveal blood is generally poor, some patients have excellent return of vision.

RECENT ADVANCES in vitreoretinal surgical techniques have made it possible to remove blood from the subretinal space in the macular area.[1-4] Some patients who have undergone surgery to remove subretinal blood showed improved vision.[2,3] An experimental model of subretinal hemorrhage showed that photoreceptor damage occurs within 24 hours.[5] Perhaps early removal of blood could prevent the visual loss associated with this condition.

To determine which patients might benefit from surgical removal of blood from the subretinal space, one must understand the natural history of the condition. Factors that might influence prognosis, such as the cause and size of the hemorrhage, have not been systematically evaluated. A common cause of subretinal hemorrhage is choroidal neovascularization associated with aging macular degeneration. This neovascularization has a poor visual prognosis.[6,7] Therefore, an eye that has a subfoveal hemorrhage associated with this type of neovascularization may also fare poorly. A similar hemorrhage caused by another process, such as trauma, might have a different prognosis. We undertook a retrospective study of subretinal hemorrhages of at least one disk diameter in size involving the center of the fovea to evaluate factors that might influence the visual prognosis.

Material and Methods

Patient records were identified by a computerized diagnostic retrieval system. Information about approximately 60,000 patients who have had fundus photography at the University of Iowa is contained in the system indexed by coded diagnoses and descriptive terms. The index was searched to identify patients with subretinal hemorrhages. To be included in the study, a patient had to have a subretinal hemorrhage of at least one disk diameter in greatest dimension that involved the center of the fovea. Patients with hemorrhage that was beneath the retinal pigment epithelium or in the vitreous were excluded. Also excluded were patients in whom the hemorrhage did not seem to be the

Accepted for publication Oct. 19, 1989.

From the Department of Ophthalmology, University of Iowa, Iowa City, Iowa (Drs. Bennett, Folk, and Blodi) and the College of Business Administration, Drake University, Des Moines, Iowa (Dr. Klugman). This study was presented in part at the annual meeting of the Association for Research in Vision and Ophthalmology, Sarasota, Florida, May 2, 1989. This study was supported in part by an unrestricted grant from Research to Prevent Blindness, Inc., New York, New York, and the Retina Research Fund of the University of Iowa.

Reprint requests to Christopher F. Blodi, M.D., Department of Ophthalmology, University of Iowa Hospitals, Iowa City, IA 52242.

major factor in the visual loss at the time of diagnosis. For example, if a patient had a large choroidal neovascular membrane with a small rim of hemorrhage, that patient was excluded. At least six months of follow-up information had to be available. A total of 29 patients who met all of the above criteria were identified.

Grading of size and thickness of subretinal hemorrhage was based on the fundus photographs. Stereophotographs were available in 28 of the 29 patients. The largest diameter of the hemorrhage was measured with a reticule and divided by the diameter of the disk. Hemorrhages greater than 4 disk diameters in largest diameter were considered large. To be classified as thick, the hemorrhage had to cause an obvious elevation of the retina (Figure). Thickness was assessed at the center of the fovea.

Visual acuity was obtained using Snellen charts with the patient's spectacle correction. If a pinhole improved the vision, that vision was used in the study. In some patients, a Snellen equivalent of 20/500 size was used to quantify poor visual acuity. The letter was held progressively closer to the patient until its orientation could be identified, and the Snellen equivalent was calculated from that distance. In charts where counting fingers at a given distance was the only recorded visual acuity, an approximation of the 20/200 Snellen equivalent at the given distance was used to analyze the data. The minimal angle of resolution is the inverse of the Snellen fraction. A visual acuity of hand

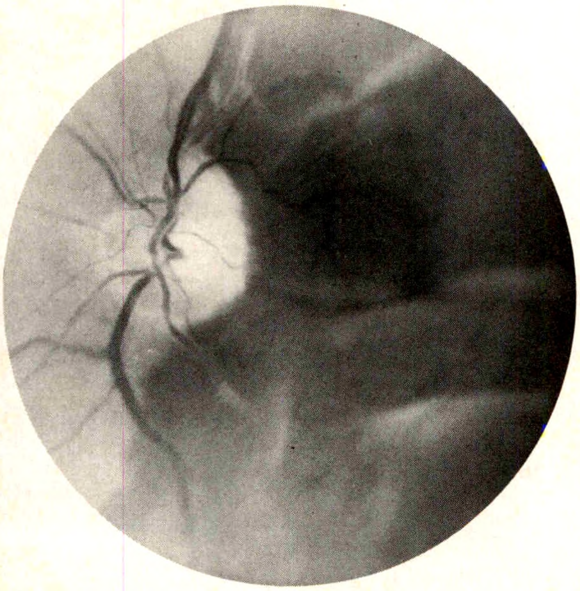


Figure (Bennett and associates). Elevation and folding of retina caused by thick subretinal hemorrhage.

motions was assigned a minimal angle of resolution of 5,600 (20/10,000). A visual acuity of light perception was assigned a minimum angle of resolution of 1,000 (20/20,000). A visual acuity of uncentral, unsteady, and unmaintained was assigned a minimal angle of resolution equal to light perception. All visual acuities were converted to the logarithm of the minimum angle of resolution for statistical analysis.[8] Initial visual acuity was compared to final visual acuity using Student's paired *t*-test. The mean of each group evaluated was compared using Student's two sample *t*-test. A loglinear model was used to compare the diagnosis of aging macular degeneration with the thickness of the hemorrhage as a predictor of the outcome of legal blindness (a visual acuity of 20/200 or worse). After statistical manipulation, visual acuities were converted back to the Snellen equivalent for ease of understanding, and these are reported herein.

Results

A total of 29 patients met the criteria for entrance in the study. Patients with subretinal hemorrhage seen at our institution were underrepresented because many patients with subretinal hemorrhage had not been photographed at their initial examination. Especially underrepresented were patients with subretinal hemorrhage after retinal detachment surgery. The average follow-up time available on patients in the study was three years. The size of the hemorrhage, cause of the hemorrhage, initial visual acuity, and final visual acuity for each patient are summarized in Table 1.

The average visual acuity at the initial visit for the entire study population was 20/860. The visual acuity tended to improve to an average final acuity of 20/480 (P = .07). Initial and final visual acuities for various groups and the P value for the change in acuities are summarized in Table 2. The patients who did not have aging macular degeneration showed significant improvement in their visual acuities, from 20/650 to 20/200, regardless of the size of the hemorrhage (P = .006). Patients with aging macular degeneration tended to worsen slightly from 20/1,300 to 20/1,700 (P = .49). The poorer visual acuity in patients with aging macular degeneration compared to those with other diagnoses was not significant at the initial examination (P = .23), but was highly significant at the final examination (P = .002). Com-

TABLE 1
PATIENT INFORMATION

PATIENT NO., AGE (YRS), SEX	DIAGNOSIS	HEMORRHAGE		VISUAL ACUITY*		FOLLOW-UP (MOS)
		SIZE	THICKNESS	INITIAL	FINAL	
1, 20, M	Trauma	Large	Thin	20/200	20/50	6
2, 25, M	Trauma	Large	Thin	20/500	20/30	66
3, 25, M	Trauma	Small	Thin	20/70	20/40	6
4, 13, M	Trauma	Small	Thin	20/500	20/30	6
5, 15, M	Trauma	Small	Thin	20/500	20/30	9
6, 78, F	Aging macular degeneration	Large	Thin	20/500	20/2,000	11
7, 82, M	Aging macular degeneration	Large	Thick	CF (2 ft)	CF (2 ft)	53
8, 70, F	Aging macular degeneration	Large	Thick	CF (1 ft)	CF (3 ft)	14
9, 85, F	Aging macular degeneration	Large	Thin	20/500	CF (4 ft)	67
10, 78, F	Aging macular degeneration	Large	Thin	20/300	20/200	12
11, 60, M	Aging macular degeneration	Small	Thin	20/1000	20/300	27
12, 70, M	Aging macular degeneration	Small	Thin	20/500	LP	32
13, 77, F	Aging macular degeneration	Small	Thin	20/500	20/3,000	9
14, 54, M	Aging macular degeneration	Large	Thick	LP	20/8,000	10
15, 71, M	Aging macular degeneration	Large	Thick	20/500	20/320	25
16, 57, F	Aging macular degeneration	Large	Thick	CF (3 ft)	CF (3 ft)	108
17, 62, F	Aging macular degeneration	Large	Thick	HM	HM	84
18, 51, M	Idiopathic disease	Large	Thick	CF (4 ft)	20/70	77
19, 6 wks, M	Infant trauma	Large	Thick	Uncentral, unsteady, unmaintained	CF (6 ft)	36
20, 1, M	Infant trauma	Large	Thick	Uncentral, unsteady, unmaintained	Uncentral, unsteady, unmaintained	24
21, 70, F	Macroaneurysm	Small	Thick	CF (2 ft)	20/3,000	10
22, 57, M	Macroaneurysm	Small	Thick	20/200	20/400	36
23, 77, M	Macroaneurysm	Small	Thin	20/500	20/1,000	16
24, 82, F	Macroaneurysm	Small	Thick	CF (3 ft)	20/200	11
25, 51, M	Presumed ocular histoplasmosis syndrome	Large	Thin	20/2,000	20/200	41
26, 50, M	Presumed ocular histoplasmosis syndrome	Small	Thin	20/200	20/30	62
27, 46, F	Presumed ocular histoplasmosis syndrome	Small	Thin	20/200	CF (4 ft)	144
28, 18, M	Pseudoxanthoma elasticum	Large	Thin	20/200	20/2,000	29
29, 78, F	Scleral buckle	Large	Thin	20/200	20/70	29

*LP indicates light perception; CF, counting fingers; HM, hand motions.

parisons of the visual outcome of various groups of patients are summarized in Table 3. The other diagnosis that seemed to affect the prognosis was that of choroidal rupture in adults. These patients showed remarkable improvement to an average final visual acuity of 20/35 ($P = .01$), and this visual outcome was significantly better than that in the other patients ($P < .001$).

The size of the hemorrhage also had a significant impact on the visual acuity. Both the area covered by the hemorrhage and the thickness of the hemorrhage had a significant effect on the initial visual acuity. The average initial visual acuity of those patients with a hemorrhage more than 4 disk diameters in greatest diameter was 20/1,380, whereas the average for those with a smaller area of hemorrhage was 20/430 ($P = .039$). This difference between large and small hemorrhages, however, was not maintained in the final visual acuities (20/600 vs 20/350, $P = .51$). Patients with thick hemorrhages had significantly worse initial visual acuities (20/2,800) than patients with thin hemorrhages (20/370, $P < .001$). The worst visual acuity was also present at the final exam-

TABLE 2
COMPARISONS OF INITIAL AND FINAL VISUAL ACUITIES

PATIENT GROUP (NO.)	VISUAL ACUITY INITIAL	VISUAL ACUITY FINAL	P VALUE
All patients (29)	20/860	20/480	.07
Aging macular degeneration (12)	20/1,300	20/1,700	.49
Non-aging macular degeneration patients (17)	20/650	20/200	.006
Adult choroidal rupture (5)	20/280	20/35	.01
Thick hemorrhage (12)	20/2,800	20/1,300	.06
Non-aging macular degeneration thick hemorrhages (6)	20/2,400	20/800	.17
Aging macular degeneration thick hemorrhages (6)	20/3,200	20/2,100	.10
Thin hemorrhages (17)	20/370	20/240	.36
Non-aging macular degeneration thin hemorrhages (11)	20/320	20/90	.02
Aging macular degeneration thin hemorrhages (6)	20/520	20/1,400	.22
Large hemorrhages (17)	20/1,400	20/600	.02
Small hemorrhages (12)	20/440	20/360	.75

ination (20/1,300 vs 20/240, P = .02). Patients with thick hemorrhages, however, showed an improvement from initial to final visual acuity that approached statistical significance (P = .06). The difference in visual outcome between thick and thin hemorrhages was still significant when patients with aging macular degeneration were excluded from the calculations (20/800 vs 20/90, P = .02).

To determine which factor had the most impact on the final visual acuity, we used a loglinear model to compare the predictive value of the diagnosis of aging macular degeneration vs the presence of a thick hemorrhage to the outcome of legal blindness. The diagnosis of aging macular degeneration was the significantly more important predictor (P = .03).

Discussion

In this study, patients with aging macular degeneration had poor initial visual acuity and did not change on follow-up, whereas other patients improved significantly. The final visual acuity in patients with aging macular degeneration was significantly worse than that in the rest of the group. A loglinear model also showed that the diagnosis of aging macular degeneration was a more important predictor of poor final vision than was the thickness of the hemorrhage.

Gass[9] noted that the visual prognosis is better when the hemorrhage is subretinal than when it is below the retinal pigment epithelium. He observed that when patients with subretinal neovascularization from aging macular degeneration bleed, the blood spreads beneath the retinal pigment epithelium and only secondarily breaks through into the subretinal space.[10] In other conditions, such as trauma or the presumed ocular histoplasmosis syndrome, the hemorrhage is present almost exclusively in the subretinal space.[11,12] Our data support the idea that patients with aging macular degeneration fare poorly when choroidal neovascular membranes bleed, even though we excluded patients with hemorrhages below the retinal pigment epithelium. In patients in whom the blood was thick, however, it was impossible to see through the subretinal blood to evaluate for the presence of hemorrhage below the retinal pigment epithelium. Therefore, some or all of our patients with thick hemorrhages may have also had hemorrhages beneath the retinal pigment epithelium. Alternatively, the retina and retinal pigment epithelium may be compromised by the condition of aging macular degeneration so that blood is poorly tolerated. It is also possible that the process of neovascularization in aging

TABLE 3
COMPARISONS BETWEEN VISUAL OUTCOME

GROUP (FINAL VISUAL ACUITY)	GROUP (FINAL VISUAL ACUITY)	P VALUE
Large hemorrhage (20/600)	Small hemorrhage (20/350)	.51
Thick hemorrhage (20/1,300)	Thin hemorrhage (20/240)	.02
Non-aging macular degeneration with thick hemorrhage (20/800)	Non-aging macular degeneration with thin hemorrhage (20/90)	.02
Aging macular degeneration (20/1,700)	Non-aging macular degeneration (20/200)	.002
Aging macular degeneration (20/1,700)	Choroidal rupture (20/35)	<.001
Aging macular degeneration with thin hemorrhage (20/1,400)	Non-aging macular degeneration with thin hemorrhage (20/90)	.003
Aging macular degeneration with thick hemorrhage (20/2,100)	Non-aging macular degeneration with thick hemorrhage (20/800)	.33
Choroidal rupture (20/35)	Nonchoroidal rupture (20/830)	<.001

macular degeneration may cause more scarring and disruption of the photoreceptors. Regardless of the mechanism, it appears that patients with aging macular degeneration have a worse prognosis from subretinal hemorrhage than do patients with other conditions.

The thickness of the hemorrhage appeared to have more impact on the final visual acuity than did the area of hemorrhage, though both had significant effect on the initial vision. Glatt and Machemer[5] postulated that one mechanism of the damage of subretinal blood is a barrier effect that prevents the photoreceptors from receiving metabolic support from the retinal pigment epithelium and choroid. Our observations support this theory, because a thick hemorrhage would be a more complete barrier and lead to more irreversible damage. The patients who did not have aging macular degeneration and had a thin hemorrhage showed remarkable improvement. The average final visual acuity in this group was 20/90. A thin hemorrhage, therefore, might be a less effective barrier and cause dysfunction that is partially reversible.

The natural course of the hemorrhages in patients not affected with aging macular degeneration was improvement in vision. Even in the group with thick hemorrhages, including some patients with aging macular degeneration, there tended to be improvement. Though experimental models have shown irreversible photoreceptor damage from subretinal blood,[5] perhaps the damage is not complete under the entire hemorrhage. Alternatively, patients may learn to compensate by fixating around a scotoma, improving their measured visual acuity in spite of irreversible damage.

The number of patients in this study was small, and the results must be interpreted cautiously because of its retrospective design. It appears, however, that there are substantial differences in the outcome of patients with subretinal hemorrhages depending on cause and size of the hemorrhage. The diagnosis of aging macular degeneration appears to be associated with a poor prognosis. The thickness of the hemorrhage also may be an independent prognostic factor. In patients other than those with aging macular degeneration, however, the condition usually improves. In patients with thin hemorrhages, the return of vision can be excellent.

In considering patients for surgery, one would like to select those with the worst prognosis, that is, those with aging macular degeneration. In such patients, however, the blood may be partially below the retinal pigment epithelium. Even if the blood is removed, the remaining neovascular membrane may cause significant scarring and visual loss. Conversely, patients with thin hemorrhages from trauma appear to do well; they have excellent return of vision and would not be good candidates for intervention. Because even the group with thick hemorrhages, including those patients with aging macular degeneration, tended to improve, the inclusion of untreated controls in any study of surgical intervention for subretinal blood is necessary.

References

1. Abrams, G. A.: Retinotomies and retinectomies. In Ryan, S. J. (ed.): Retina, vol. 3. St. Louis, C. V. Mosby, 1989, pp. 321–322.

2. De Juan, E., and Machemer, R.: Vitreous surgery for hemorrhagic and fibrous complications of age-related macular degeneration. Am. J. Ophthalmol. 105:25, 1988.

3. Hanscom, T. A., and Diddie, K. R.: Early surgical drainage of macular subretinal hemorrhage. Arch. Ophthalmol. 105:1722, 1987.

4. Flynn, H. W., Davis, J. L., Parel, J. M., and Lee, W. G.: Applications of a cannulated extrusion needle during vitreoretinal microsurgery. Retina 8:42, 1988.

5. Glatt, H., and Machemer, R.: Experimental subretinal hemorrhage in rabbits. Am. J. Ophthalmol. 94:762, 1982.

6. Bressler, S. B., Bressler, N. M., Fine, S. L., Hillis, A., Murphy, R. P., Olk, R. J., and Patz, A.: Natural course of choroidal neovascular membranes within the foveal avascular zone in senile macular degeneration. Am. J. Ophthalmol. 93:157, 1982.

7. Bressler, S. B., Bressler, N. M., Fine, S. L., McCormick, P., and Auer, C.: Subfoveal neovascular membranes in senile macular degeneration. Relationship between membrane size and visual prognosis. Retina 3:7, 1983.

8. Westheimer, G.: Scaling of visual acuity measurements. Arch. Ophthalmol. 97:327, 1979.

9. Gass, J. D M.: Stereoscopic Atlas of Macular Diseases, ed. 3. St. Louis, C. V. Mosby, 1987, p. 80.

10. ———: Pathogenesis of disciform detachment of the neuroepithelium. III. Senile disciform macular degeneration. Am. J. Ophthalmol. 63:617, 1967.

11. ———: Pathogenesis of disciform detachment of the neuroepithelium. V. Disciform macular degeneration secondary to focal choroiditis. Am. J. Ophthalmol. 63:661, 1967.

12. ———: Pathogenesis of disciform detachment of the neuroepithelium. VI. Disciform detachment secondary to heredodegenerative, neoplastic and traumatic lesions of the choroid. Am. J. Ophthalmol. 63:689, 1967.

Drusen as Risk Factors in Age-Related Macular Disease

D. Pauleikhoff, M.D., M. J. Barondes, M.D., D. Minassian, M.Sc.,
I. H. Chisholm, M.B.B.S., and A. C. Bird, M.D.

In a study of 150 consecutive patients with age-related macular disease and unilateral visual loss, the drusen in the better eye were analyzed for size, number, density, and fluorescein angiographic appearance, and these characteristics were compared with the type of the lesion causing visual loss in the contralateral eye. In the fellow eye of an eye with avascular detachment of the retinal pigment epithelium, the drusen were more densely packed, larger, and less fluorescent than in the fellow eye of an eye with primary neovascularization. The characteristics of drusen in fellow eyes of those eyes with pigment epithelial detachments and evidence of subpigment epithelial new vessels were intermediate between the other two groups. Because there is significant symmetry of drusen between fellow eyes, these data imply that the characteristics of drusen are important in the determination of the form of the lesion complicating age-related macular disease.

AGE-RELATED MACULAR DISEASE is now the most common cause of registered blindness in the western countries,[1-6] but its pathogenesis is still unknown. The lesions that are believed to cause loss of central vision are detachment of the pigment epithelium and the new vessel growth between Bruch's membrane and the retina.[7]

Changes in the retinal pigment epithelium and Bruch's membrane throughout life are believed to be important in the development of this disease.[8-14] These changes are the result of the accumulation of material released from the pigment epithelial cells in Bruch's membrane.[15-18] Drusen represent the clinical correlate of this process.[7,8,11]

There is evidence that the density, size, and fluorescence of drusen may determine both the magnitude of risk of visual loss and the type of the exudative lesion causing that loss. For example, eyes with large drusen are at higher risk of losing vision than those with small drusen, and retinal pigment epithelial detachments occur in eyes with drusen that are hypofluorescent on fluorescein angiographic examination.[19-25] These conclusions, however, were largely derived from evidence of retrospective studies in which the data were often incomplete or the definitions of the fundus lesions were imprecise, and in some surveys, the number of patients was small.

Histologic studies have shown that there are different morphologic types of drusen,[11,26] and wide variation in the appearance, distribution, and fluorescence of drusen have been recorded. Considerable symmetry of drusen characteristics, however, has been shown between fellow eyes.[4,21,27-30] This symmetry implies that the drusen in the fellow eye of an eye with visual loss would give some indication of the characteristics of the drusen that predated the development of the lesion in the first eye.

If these assumptions are correct, some correlation might be expected between the characteristics of drusen in one eye and the form of the macular lesion in the other eye in patients with unilateral visual loss.

Subjects and Methods

The clinical records, color photographs, and fluorescein angiograms of 150 consecutive patients recruited to a prospective study of age-related macular disease were reviewed. In one eye of each patient, there was visual loss caused

Accepted for publication Sept. 12, 1989.
From the Departments of Clinical Ophthalmology (Drs. Pauleikhoff and Barondes, Mr. Chisholm, and Dr. Bird) and Preventative Ophthalmology (Mr. Minassian), Institute of Ophthalmology, London, England. This study was supported by the Medical Research Council, Grant No. G8709312, and by Deutsche Forschungsgemeinschaft and Wacker Foundation (Dr. Pauleikhoff).
Reprint requests to A. C. Bird, Institute of Ophthalmology, Moorfields Eye Hospital, City Road, London EC 1 V 2PD, United Kingdom.

by pigment epithelium detachment, choroidal neovascularization, or disciform scars. The other eye had good visual acuity (better than 20/20), and there were drusen only in the fundus.

Color photographs and fluorescein angiograms of the fellow eye with drusen in each patient were analyzed by two of us (D.P. and M.J.B.) independently for number, size, density, and early and late angiographic fluorescence of the macular drusen by using a previously reported grading scheme.[20,25,30] The posterior pole was divided into two regions: a central area within 1,600 μm of the fovea and a peripheral area between 1,600 and 2,800 μm of the foveola. The drusen were analyzed according to their number in each region (less than ten, between ten and 20, and more than 20), and to their size (less than 50 μm, between 50 and 500 μm, and greater than 500 μm). The density was classified as scattered if the drusen were distinct one from another, subconfluent if the drusen borders were just touching, and confluent if the borders overlapped. Fluorescence of drusen was assessed as equal to choroidal fluorescence, slightly brighter than choroidal fluorescence, or brightly fluorescent. In most cases, the drusen were uniform in size, distribution, and fluorescence in each area of the macula. When this was not the case, the classification was determined by the largest, most densely packed, and most fluorescent lesions. If disagreement occurred between the two readers, a third observer was asked to arbitrate, and the results were assigned after discussion.

The clinical data and the results of the analysis of drusen characteristics in the fellow eye were recorded and analyzed statistically. The reliability of the analysis was examined by recording the percentage agreement for each item between the two independent observers.

To compare specified groups, patients were subdivided according to the nature of the lesion in the eye with visual loss. The first subgroup consisted of patients with avascular pigment epithelial detachments. The second subgroup comprised those with pigment epithelium detachments and evidence of neovascularization in the subpigment epithelial space, which was deemed to be the case if lipid exudates, blood, or notching were seen on ophthalmoscopic examination, or if angiography disclosed irregular fluorescence not explained by irregular pigment in the detached tissue. In the third group, there was well-defined subretinal neovascular tissue seen in the angiogram early in the study, with increasing fluorescence as the study progressed. A fourth group included those lesions with early hyperfluorescence without dye leakage in the late phase of fluorescein angiography, or with an isolated spot of hyperfluorescence leakage only in the late phase of the angiogram; these lesions were designated as having occult or ill-defined choroidal neovascularization.[31,32] In the fifth group were lesions with old fibrous subretinal disciform scars in which there was no indication of the nature of the initial lesion.

An association between the specific characteristics of drusen in one eye and the type of the macular lesion in the other were evaluated by chi-square tests applied to the cross-tabulated data.[33] Thus the drusen characteristics of the various subgroups defined by the type of macular lesions were compared.

TABLE 1
NUMBER OF DRUSEN

	NONE	<10	10–20	>20
Pigment epithelial detachments (Group 1)				
Central	—	—	—	100%
Peripheral	4%	44%	8%	44%
Pigment epithelial detachments and new vessels (Group 2)				
Central	—	—	12%	88%
Peripheral	17%	25%	29%	29%
Manifest new vessels (Group 3)				
Central	—	11%	9%	80%
Peripheral	19%	29%	22%	30%
Others (Groups 4 and 5)				
Central	—	10%	13%	77%
Peripheral	17%	25%	25%	33%

TABLE 2
SIZE OF DRUSEN

	NONE	<50 μM	50-500 μM	>500 μM
Pigment epithelial detachments (Group 1)				
Central	—	—	52%	48%
Peripheral	4%	28%	68%	—
Pigment epithelial detachment and new vessels (Group 2)				
Central	—	—	92%	8%
Peripheral	17%	21%	62%	—
Manifest new vessels (Group 3)				
Central	—	12%	82%	6%
Peripheral	19%	34%	47%	—
Others (Groups 4 and 5)				
Central	—	10%	12%	78%
Peripheral	18%	25%	25%	32%

Results

Of the 150 patients, 91 (60.7%) were women and 59 (39.3%) men. The average age at initial examination was 70.8 years, with a range of 50 to 89 years.

For the different drusen characteristics, the interobserver agreement was 93.3% for the number of drusen, 91.7% for size, 88.5% for the density, and 84.8% and 94.0% for early and late fluorescence of drusen.

In the eye with visual loss, 25 patients (16.7%) had avascular pigment epithelial detachments (Group 1), 24 (16.0%) had vascular pigment epithelial detachments (Group 2), 65 (43.3%) had primary neovascular lesions (Group 3), six (4%) had occult neovascularization, and 30 (20%) had fibrous scars of indeterminate origin (others). The characteristics of drusen in the fellow eyes grouped according to the nature of the lesion in the other eye are summarized in Tables 1 through 4.

Statistical analysis of the drusen characteristics was undertaken. We compared Group 1, in which pigment epithelial detachment appeared to be the primary event, with Group 3, in which neovascularization initiated the disorder (Table 5). Fellow eyes of patients in Group 1 showed significantly larger, more densely packed, and less early and late fluorescent drusen than in fellow eyes of patients in Group 3.

Groups 1 and 3 were compared with Group 2 with vascular pigment epithelial detachments.

TABLE 3
DENSITY OF DRUSEN

	NONE	SCATTERED	SUBCONFLUENT	CONFLUENT
Pigment epithelial detachments (Group 1)				
Central	—	—	20%	80%
Peripheral	4%	36%	56%	4%
Pigment epithelial detachment and new vessels (Group 2)				
Central	—	8%	63%	29%
Peripheral	17%	33%	50%	—
Manifest new vessels (Group 3)				
Central	—	15%	74%	11%
Peripheral	19%	49%	32%	—
Others (Groups 4 and 5)				
Central	—	17%	64%	19%
Peripheral	17%	53%	30%	—

TABLE 4
EARLY AND LATE FLUORESCENCE OF DRUSEN

	NO MORE FLUORESCENT THAN CHOROID	SLIGHTLY MORE FLUORESCENT THAN CHOROID	BRIGHTLY FLUORESCENT
	EARLY / LATE	EARLY / LATE	EARLY / LATE
Pigment epithelial detachments (Group 1)			
Central	12% / —	88% / 73%	— / 27%
Peripheral	— / —	75% / 62%	25% / 38%
Pigment epithelial detachment and new vessels (Group 2)			
Central	— / —	75% / 48%	25% / 52%
Peripheral	— / —	67% / 39%	33% / 61%
Manifest new vessels (Group 3)			
Central	— / —	44% / 34%	56% / 66%
Peripheral	— / —	50% / 25%	50% / 75%
Others (Groups 4 and 5)			
Central	4% / —	18% / 27%	78% / 73%
Peripheral	— / —	22% / 22%	78% / 78%

The characteristics of drusen in Group 2 were mid-way between the other two groups, although significant differences were found in few analyses (Table 2). The remaining two groups were not analyzed because the number with occult neovascularization was small, and the initiating process in those with disciform scars was uncertain.

Discussion

The interobserver reliability in this study of between 85% and 95% is comparable to other studies[34] and has been considered to be an acceptable degree of agreement.[23] The correlation of drusen characteristics in one eye and the form of macular lesion in the fellow eye has some relevance to the current concepts of pathogenesis of age-related macular disease.

The wide variation of the clinical and histopathologic appearance and the distribution of drusen[11,25,26,35] suggests that material accumulating with age in Bruch's membrane may be the result of failure of several different metabolic systems. By inference, differences in drusen characteristics from one patient to another may reflect a metabolic deficit specific to one of the patients. The results of this study and recent evidence imply that variation in the chemical

TABLE 5
STATISTICAL DIFFERENCES OF DRUSEN CHARACTERISTICS BETWEEN GROUPS

	GROUPS 1 AND 3	GROUPS 1 AND 2	GROUPS 2 AND 3
Number			
Central	—	—	—
Peripheral	—	—	—
Size			
Central	P < .005	P < .005	—
Peripheral	—	—	—
Density			
Central	P < .005	P < .005	P < .05
Peripheral	P < .05	—	—
Early fluorescence			
Central	P < .005	—	—
Peripheral	—	—	—
Late fluorescence			
Central	P < .005	—	—
Peripheral	P < .05	—	—

composition of drusen may influence the form of the lesion that may result and the magnitude risk of such event occurring.[25,35]

The considerable symmetry of drusen between fellow eyes[4,21,27-30] indicates that the drusen that existed in the eye that had lost vision would have been similar to those observed in the fellow eye. It can be deduced that the correlations identified imply a causal relationship between the drusen characteristics and the form of the sight-impairing lesion. It may be concluded, therefore, that densely packed and relatively hypofluorescent drusen cause retinal pigment epithelial detachments, a conclusion which parallels the results of a previous study.[25] It is also evident that in the presence of relatively hyperfluorescent drusen, it is more likely that the lesion causing visual loss would be choroidal neovascularization rather than detachment of the retinal pigment epithelium.

The patients who had pigment epithelial detachment with new vessels in the subpigment epithelial space were different from the other two groups. It is possible that these patients represented two populations, one in which the lesion was initiated by neovascularization, and the other in which pigment epithelial detachment was the first event, and blood vessel growth occurred as a secondary response. Alternatively, they may be a single intermediate group. The data did not allow a distinction to be made between these two possibilities.

These observations are in accord with proposals about the pathogenesis of detachment of the pigment epithelium and its relationship to the hydraulic conductivity of Bruch's membrane.[25,35,36] According to these concepts, hypofluorescent drusen imply the presence of lipids, particularly neutral fats, which decrease hydraulic conductivity. This decrease in conductivity would result in the accumulation of fluid derived from the pigment epithelium between the pigment epithelium and Bruch's membrane.

Another possible consequence of the variable content of drusen may be alteration of the magnitude of risk of visual loss. A preliminary study suggests that large differences may exist between different groups. With one exception, all studies have shown the risk of visual loss in the second eye to be between 10% and 12% per year.[19-21,24] In the fellow eye of a tear of detached pigment epithelium, this risk appears to be much higher.[37,38]

These data imply that age-related macular disease and, in particular, the changes in Bruch's membrane that induce exudative lesions should not be regarded as a single process. Future studies should take into account these potential variations, specifically the characteristics of drusen and the nature of the initiating event.

References

1. Sorsby, A.: Reports on Public Health and Medical Subjects. London, HMSO, 1966.

2. Kahn, H. A., and Moorhead, H. B.: Statistics on Blindness in the Model Reporting Areas 1969-70. United States Department of Health, Education and Welfare Publication No. (NIH) 73-427. Washington, D.C., U.S. Government Printing Office, 1973.

3. Ghafour, M., Allan, D., and Foulds, W. S.: Common causes of blindness and visual handicap in the west of Scotland. Br. J. Ophthalmol. 167:209, 1988.

4. Leibowitz, H., Krueger, D. E., Maunder, L. R., Milton, R. C., Kini, M. M., Kahn, H. A., Mickerson, R. J., Pool, J., Colton, T. L., Ganley, J. P., Loewenstein, J. I., and Dawber, T. R.: The Framingham eye study monograph. An ophthalmological and epidemiological study of cataract, glaucoma, diabetic retinopathy, macular degeneration and visual acuity in a general population of 2631 adults, 1973-75. Surv. Ophthalmol. 25(suppl):335, 1984.

5. Grey, R. H B., Burns-Cox, C. J., and Hughes, A.: Blind and partially sighted registration in Avon. Br. J. Ophthalmol. 73:988, 1989.

6. Thompson, J. R., and Rosenthal, A. R.: Recent trends in the registration of blindness and partial sight in Leicester. Br. J. Ophthalmol. 73:95, 1989.

7. Bressler, N. M., Bressler, S. B., and Fine, S. L.: Age related macular degeneration. Surv. Ophthalmol. 32:375, 1988.

8. Young, R. W.: Pathology of age related macular disease. Surv. Ophthalmol. 31:291, 1987.

9. Hogan, M. J., and Alvarado, J.: Studies on the human macula. IV. Aging changes in Bruch's membrane. Arch. Ophthalmol. 77:410, 1967.

10. Sarks, S. H.: Ageing and degeneration in the macular region. A clinico-pathological study. Br. J. Ophthalmol. 60:324, 1967.

11. Green, W. R., and Key, S. N.: Senile macular degeneration. A histopathological study. Trans. Am. Ophthalmol. Soc. 75:180, 1977.

12. Grindle, C. F J., and Marshall, J.: Aging changes in Bruch's membrane and their functional implications. Trans. Ophthalmol. Soc. U.K. 98:172, 1978.

13. Killingworth, M. C.: Age-related components of Bruch's membrane in the human eye. Graefes Arch. Clin. Exp. Ophthalmol. 225:406, 1987.

14. Feeney-Burns, L., Gao, C. L., and Tidwell, M.: Lysosomal enzyme cytochemistry of human RPE, Bruch's membrane and drusen. Invest. Ophthalmol. Vis. Sci. 28:1138, 1987.

15. Feeney-Burns, L., and Ellersieck, M. R.: Age-related changes in the ultrastructure of Bruch's membrane. Am. J. Ophthalmol. 100:686, 1985.

16. Reme, C.: Autophagy in visual cells and pigment epithelium. Invest. Ophthalmol. 16:177, 1977.
17. Ishibashi, T., Sorgente, N., Patterson, R., and Ryan, S. J.: Pathogenesis of drusen in the primate. Invest. Ophthalmol. Vis. Sci. 27:184, 1986.
18. Burns, R. P., and Feeney-Burns, L.: Clinicomorphological correlations of drusen and Bruch's membrane. Trans. Am. Ophthalmol. Soc. 78:206, 1980.
19. Strahlmann, E. R., Fine, S. L., and Hillis, A.: The second eye of patients with senile macular degeneration. Arch. Ophthalmol. 101:1191, 1983.
20. Gregor, Z., Bird, A. C., and Chisholm, I. H.: Senile disciform macular degeneration in the second eye. Br. J. Ophthalmol. 61:141, 1977.
21. Gass, J. D M.: Drusen and disciform macular detachment and degeneration. Arch. Ophthalmol. 90:206, 1973.
22. Smiddy, W. E., and Fine, S. L.: Prognosis of patients with bilateral macular drusen. Ophthalmology 91:271, 1984.
23. Bressler, S. B., Bressler, N. M., Seddon, J. M., Gragoudas, E. S., and Jacobson, L. P.: Drusen characteristics in patients with exudative versus nonexudative age-related macular degeneration. Retina 8:109, 1988.
24. Gragoudas, E. S., and Chandra, S. R.: Disciform degeneration of the macula. II. Pathogenesis. Arch. Ophthalmol. 94:755, 1976.
25. Chuang, E. L., and Bird, A. C.: The pathogenesis of tears of the retinal pigment epithelium. Am. J. Ophthalmol. 105:285, 1988.
26. Sarks, S. H.: Drusen and their relationship to senile macular degeneration. Aust. J. Ophthalmol. 8:117, 1980.
27. Coffey, A. J H., and Brownstein, S.: The prevalence of macular drusen in postmortem eyes. Am. J. Ophthalmol. 102:164, 1986.
28. Lewis, H., Straatsma, B. R., and Foos, R. Y.: The prevalence of macular drusen in postmortem eyes. Am. J. Ophthalmol. 102:801, 1986.
29. Lewis, H., Straatsma, B. R., and Foos, R. Y.: Chorioretinal juncture. Multiple extramacular drusen. Ophthalmology 93:1098, 1986.
30. Barondes, M. J., Pauleikhoff, D., Chisholm, I. H., and Bird, A. C.: Bilaterality of drusen. Br. J. Ophthalmol. In press.
31. Soubrane, G., and Francais, C.: Aspects atypique des néovaisseaux sous-rétinens de la dégénérescence maculaire liée à l'âge, 2, NVSR occultes. In Coscas, G., and Soubranne, G. (eds.): Néovaisseaux Sous-Rêtinens Maculaire et Laser. Paris, Doin Éditeurs, 1987, pp. 69–74.
32. Miller, H., Miller, B., and Ryan, S. J.: The role of retinal pigment epithelium in the involution of subretinal neovascularization. Invest. Ophthalmol. Vis. Sci. 27:1644, 1986.
33. Mantel, R. E., and Haenszel, W.: Statistical aspects of the analysis of data from retrospective studies of disease. J. Natl. Cancer Inst. 22:719, 1959.
34. Bressler, S. B., Bressler, N. M., Seddon, J. M., Gragoudas, E. S., and Jacobson, L. P.: Interobserver and intraobserver reliability in the clinical classification of drusen. Retina 8:102, 1988.
35. Bird, A. C., and Marshall, J.: Retinal pigment epithelial detachments in the elderly. Trans. Ophthalmol. Soc. U.K. 105:674, 1986.
36. Pauleikhoff, D., Marshall, J., and Bird, A. C.: Histochemical and morphological correlation of aging changes in Bruch's membrane. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1989, p. 153.
37. Chuang, E. L., and Bird, A. C.: Bilaterality of tears of the retinal pigment epithelium. Br. J. Ophthalmol. 72:918, 1988.
38. Schoeppner, G., Chuang, E. L., and Bird, A. C.: Retinal pigment epithelial tears. Risk to the second eye. Am. J. Ophthalmol. 108:000, 1989.

OPHTHALMIC MINIATURE

My whole name is Blinking Jack Ernest Stokes, stokes the fire, stokes the stove, stokes the fiery furnace of hell! I've got a nerve problem in back of the face so I blink. June nicknamed me for it when she was little.

Kaye Gibbons, *A Virtuous Woman*
Chapel Hill, Algonquin Books of Chapel Hill, 1989, p. 1

Autosomal Dominant Congenital Stationary Night Blindness and Normal Fundus With an Electronegative Electroretinogram

Kenneth G. Noble, M.D., Ronald E. Carr, M.D., and Irwin M. Siegel, Ph.D.

We studied three members of three successive generations of a family with autosomal dominant congenital stationary night blindness and normal fundi. Psychophysical studies on two members showed normal final cone thresholds and mildly increased rod thresholds. Full-field electroretinograms on all three members showed normal photopic b-wave amplitudes and implicit times. Under scotopic conditions, the rod response was absent, and with a bright flash stimulus, there was a normal a-wave with no b-wave. This electronegative dark-adapted electroretinogram resembled the Schubert-Bornschein type seen in congenital stationary blindness, which has been seen only in autosomal and X-linked recessive pedigrees.

CONGENITAL STATIONARY NIGHT BLINDNESS constitutes a group of inherited disorders characterized by nonprogressive night-vision loss present since birth. Patients with these disorders may be divided into two types, those with a normal-appearing fundus and those with a distinctive fundus abnormality.[1] The normal fundus may be subdivided according to the mode of inheritance, that is, autosomal dominant, autosomal recessive, and X-linked recessive.

Visual function studies have suggested the pathologic abnormality in each of these three varieties.[2-5] Although studies on dominant pedigrees have been previously reported,[2,6-9] this information is not comprehensive. We collected electrophysiologic and psychophysical data on patients from three consecutive generations who have autosomal dominant congenital stationary night blindness with normal fundi.

Accepted for publication Sept. 28, 1989.

From the Department of Ophthalmology, New York University Medical Center, New York, New York. This study was supported by a grant from the Retinitis Pigmentosa Foundation Fighting Blindness and an unrestricted grant from the Kirby Eye Institute.

Reprint requests to Kenneth G. Noble, M.D., Department of Ophthalmology, New York University Medical Center, 550 First Ave., New York, NY 10016.

Methods

Dark adaptation was performed after pupillary dilation to an average size of 8 mm and exposure to a preadaptation field of 2,000 millilamberts for seven minutes. This pre-adapting intensity (about 7 log scotopic troland seconds) was sufficient to bleach more than 99% of the available rhodopsin within the exposed retinal areas.[10] The course of adaptation was tested at 30-seconds to one-minute intervals with a 1.5-degree white target located at 15 degrees temporal to the fovea. At the conclusion of dark adaptation (30 to 35 minutes), absolute thresholds were determined across the horizontal meridian nasally and temporally from 5 degrees to 40 degrees (retinal profiles).

The procedure for obtaining electroretinographic data was described in an earlier study.[11] In brief, flashes from a Grass PS-22 photic stimulator illuminated the interior of a ganzfeld bowl. For recording the single flash and flicker cone electroretinogram, the background was set to about 300 cd/m^2, and the brightest flash setting (I 16) was used. The subject was light-adapted to background illumination at least as bright as the ganzfeld for a minimum of ten minutes before recording sessions began. Thus sufficient adaptation was allowed to maximize the cone amplitude.[12] Dark-adapted electroretinograms were recorded after the psychophysical tests of adaptometry; therefore, patients were dark-adapted for at least 40 minutes before recordings were obtained. Single-flash blue stimuli were obtained with a low (I 1) strobe

setting and a Wratten 98 gelatin filter. An electroretinographic response to a low-intensity (I 1) and a high-intensity (I 16) white flash were then obtained.

Case Reports

Information was obtained from four generations of a family in which one member each from three successive generations was symptomatic and each was examined (Patients 1, 2, and 3) (Fig. 1). No other family members were examined, and there was no history of consanguinity.

Case 1 (IV-1)

The 4-year-old boy had held all objects close to see them since 9 months of age and had been wearing spectacles since 13 months of age. The patient's mother thought that her son could not see well at night but that his peripheral vision was normal.

The corrected visual acuity was R.E.: 20/50 (−8.25 −1.25 × 125) and L.E.: 20/40 (−8.00 −1.50 × 35). The fundus showed a vertically elongated optic nerve with a mild degree of peripapillary chorioretinal atrophy but was otherwise normal. An electroretinogram showed a photopic amplitude at the lower limit of normal (100 μV) with a normal implicit time (28 msec), an absent scotopic response with a low-intensity blue stimulus, and an electronegative response (a-wave, 200 μV), with a high-intensity white stimulus after 40 minutes of dark adaptation (Fig. 2).

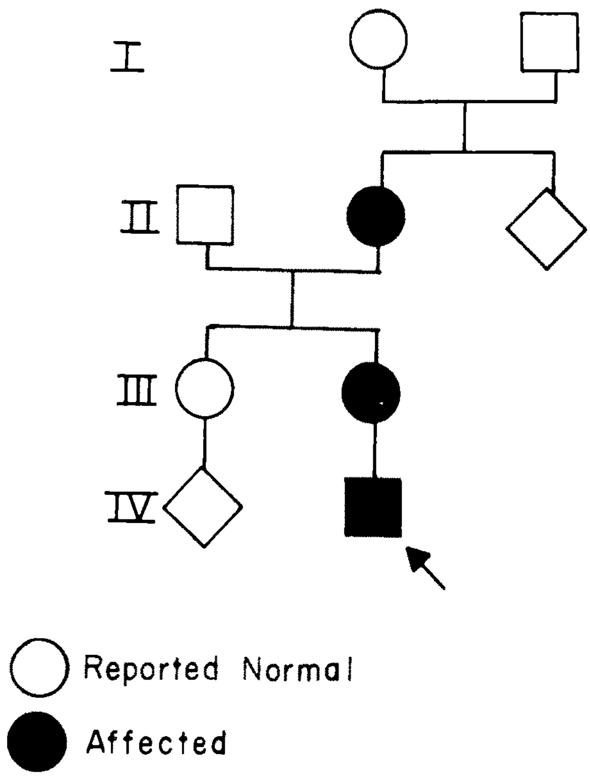


Fig. 1 (Noble, Carr, and Siegel). Family pedigree.

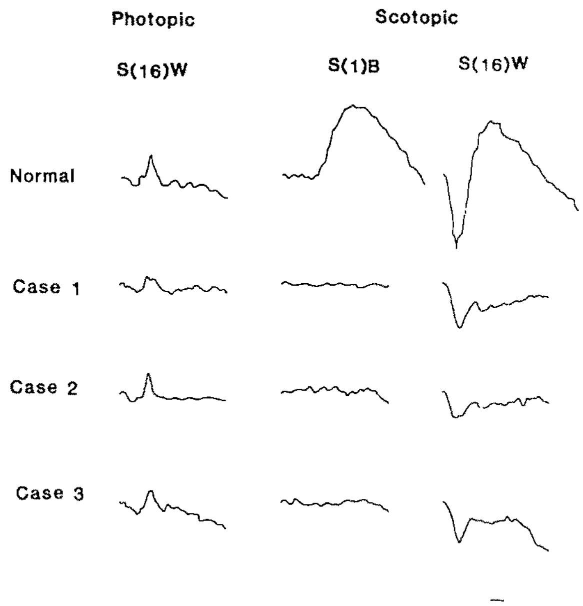


Fig. 2 (Noble, Carr, and Siegel). Electroretinogram. The electroretinographic responses are similar in all three patients. Under photopic conditions, the response to a single white flash produced a normal photopic response and implicit time. Under scotopic conditions, a low-intensity blue stimulus did not elicit a response, whereas a high-intensity white stimulus resulted in an electronegative response. The horizontal calibration designates 20 msec, the vertical calibration designates 100 μV, and the stimulus onset occurs at the beginning of the tracing. Normal photopic values are an amplitude of 140 ± 26 μV with an implicit time of 29.23 ± 2.12 msec (mean ± S.D.).

Case 2 (III-1)

The 31-year-old mother of Patient 1 had nonprogressive night vision loss noted at age 11 years. She had difficulty adapting from light to dark, but there was some improvement after ten minutes.

The corrected visual acuity was 20/20 in both eyes, and the fundus was normal. An electroretinogram was similar to her son's, with a normal photopic amplitude (130 μV) and latency (26 msec), an absent scotopic blue response, and an electronegative scotopic response (a-wave, 120 μV) with a high-intensity white stimulus after 40 minutes of dark adaptation (Fig. 2).

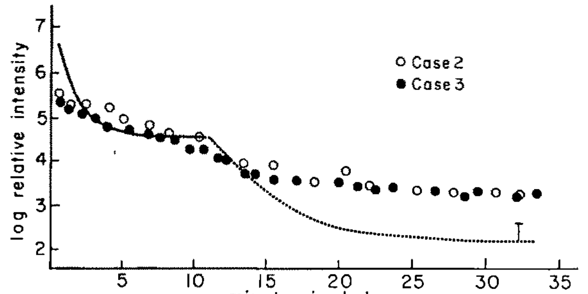


Fig. 3 (Noble, Carr, and Siegel). Dark adaptation. The dark adaptation curves of Patients 2 and 3 show a normal final cone threshold; however, the final rod thresholds are increased approximately 0.8 log unit. The dotted line represents an average curve of ten normal age-matched patients under similar testing conditions. The vertical line on the rod plateau of the normal curve represents +1 S.D. threshold variation for the full course of dark adaptation.

The dark adaptation curve showed a normal final cone threshold, but the rod thresholds at 30 to 35 minutes were increased 0.8 log unit above normal (Fig. 3). Retinal profiles confirmed the mild increase of 0.5 to 0.8 log unit above normal.

Case 3 (II-1)

The 58-year-old mother of Patient 2 and maternal grandmother of Patient 1 complained of difficulty with night vision, which was noted at age 30 years when driving at night and seemed nonprogressive. The corrected visual acuity was 20/20 in both eyes, and the fundus was normal. An electroretinogram was similar to those of Patients 1 and 2, with a normal photopic response (125-μV amplitude, 29-msec implicit time), an absent scotopic blue response, and an electronegative scotopic response (a-wave, 180 μV), with a high-intensity white stimulus after 40 minutes of dark adaptation (Fig. 2). The patient's results of dark adaptation and retinal profiles were similar to those of her daughter, with the final rod thresholds increased throughout the retina (0.5 to 0.8 log unit above normal) (Fig. 3).

Discussion

The complete genealogic record of the Nougaret family dating to the 17th century and encompassing over ten generations is the paradigm for the autosomal dominant mode of inheritance and firmly establishes this particular form of congenital stationary night blindness with a normal fundus. It is only in the last 35 years, however, that we have gained an understanding of the pathogenesis of this disorder.

The first well-documented dominant pedigree studied electrophysiologically showed a reduced but normal-appearing photopic response without a significant increase in amplitude under scotopic conditions.[6,7] These findings were confirmed by François and associates,[8] who studied three members of the Nougaret family and another dominant pedigree.[9] This type of electroretinographic response in congenital stationary night blindness has been named after the investigator, Riggs, who first described it.[7] With the exception of one possible autosomal dominant family,[13] this is the response seen in members of dominant pedigrees.

Two years before the Riggs-type electroretinogram was reported, Schubert and Bornschein[14] described a different type of response in autosomal recessive or simplex cases of congenital stationary night blindness. There was a progressive increase in the negative response (a-wave) during dark adaptation, but there was no similar increase in the positive response (b-wave). This electronegative electroretinogram in congenital stationary night blindness is referred to as the Schubert-Bornschein type and has been seen in autosomal recessive and X-linked recessive pedigrees.

With these two types of electroretinographic responses established, one study noted that both types of responses could be seen in two siblings of consanguineous parents (autosomal recessive) and in a father and a son (presumed autosomal dominant).[13] Auerbach, Godel, and Rowe believed that there was no genetic specificity associated with the electroretinographic response, although there was no genetic documentation to support this conclusion.

A recent study[15] of 64 patients with congenital stationary night blindness, normal fundi, and the Schubert-Bornschein type of electronegative electroretinogram suggested that there were two types: a complete type that lacked rod function (35 patients) and an incomplete type that showed some rod function (20 patients). None of these patients appeared to be members of autosomal dominant pedigrees.

The complete form was characterized by a monophasic dark adaptation curve consisting only of a cone branch increased about 1.0 log unit above normal; a normal scotopic electroretinographic a-wave with little b-wave activity present in the dark; only a slight reduction of the

cone electroretinogram; an average myopic correction of −10.00 diopters; and a moderate to severely reduced visual acuity. The incomplete form showed dark adaptation curves that had both cone and rod branches, though each was increased about 1.0 log unit above normal; a normal-appearing scotopic a-wave with a reduced b-wave at bright-flash intensities but at low-flash intensities small-amplitude scotopic b-waves with increased latency; severe reduction of the photopic electroretinographic responses to single-flash and flicker stimuli; a wide distribution of refractive errors; and mild-to-moderate visual acuity losses.

Although the electrical findings associated with this "complete" form of congenital stationary night blindness appear similar to those in our three patients, the dark adaptometric data are different. The cone and rod thresholds of Miyake and associates'[15] patients were markedly increased compared to ours. Figure 3 shows that the cone plateau of the curves for Patients 2 and 3 is normal, and that in contrast to the absent rod segment of the complete form, our patients clearly show a rod branch, which was increased 1.0 log unit. Although the patients with incomplete congenital stationary night blindness have rod thresholds similar to ours, their other findings, such as the increased cone thresholds and the extinguished photopic electroretinograms, make them even more difficult to compare to the patients described here.

Miyake and associates[15] suggested that the Riggs-type response, as obtained by Riggs[7] and Auerbach, Godel, and Rowe[13] in their patients, was attributable to the weaker stimulus used in their studies. They infer that with a stronger intensity stimulus, the Riggs-type response may become electronegative. They attempt to demonstrate this in their incomplete type of congenital stationary night blindness by using increasingly higher stimulus intensities to change the Riggs response into the Schubert-Bornschein response.[15] The essential feature of the Riggs-type response, however, is that under scotopic conditions this response has the wave form and temporal characteristics of a photopic response. This is not apparent in the simulated experiment. Additionally, the finding of a Riggs-type response in one family member with documented autosomal dominant disease, in which a bright-flash stimulus was used,[3] belies their hypothesis.

The findings in our three patients differ from findings in patients with complete and incomplete forms of congenital stationary night blindness described by Miyake and associates[15] because they have normal cone function. The findings in these patients further support the conclusion of Auerbach, Godel, and Rowe[13] that the type of electroretinographic response in congenital stationary night blindness is not characteristic for a particular mode of inheritance.

The electroretinographic and adaptometric results of our patients are different from those of patients of the original Nougaret pedigree[8] or patients from other reported dominant pedigrees.[3,6,7,9] Whereas the latter group had reduced b-waves under scotopic and photopic conditions, the patients we examined had fairly well-developed photopic b-waves as well as deep scotopic a-waves. The previously reported adaptometric studies of dominant congenital stationary night blindness have shown, almost without exception, increased cone thresholds and no sign of a rod branch. Results of dark adaptometry in our patients clearly show normal cone thresholds and a definite cone-rod break. Based on the electroretinographic and adaptometry findings, we believe that our pedigree represents a form of dominantly transmitted congenital stationary night blindness different from those previously described.

Fundus reflectometric studies performed on other patients with congenital stationary night blindness with normal scotopic a-waves showed normal concentration and normal bleaching kinetics of rhodopsin.[3,16] The latter findings suggested a postreceptoral neural-type disturbance. We would anticipate that because our patients had normal receptor potentials (as judged by the a-wave amplitude), they too would produce normative data in rhodopsin studies. Such studies have been useful in identifying at which retinal level the disturbance resides.

References

1. Carr, R. E.: Congenital stationary nightblindness. Trans. Am. Ophthalmol. Soc. 72:448, 1974.

2. Carr, R. E., and Siegel, I. M.: Electrophysiologic aspects of several retinal diseases. Am. J. Ophthalmol. 58:95, 1964.

3. Carr, R. E., Ripps, H., Siegel, I. M., and Weale, R. E.: Rhodopsin and the electrical activity of the retina in congenital nightblindness. Invest. Ophthalmol. 5:497, 1966.

4. ———: Visual functions in congenital nightblindness. Invest. Ophthalmol. 5:508, 1966.

5. Carr, R. E., Ripps, H., and Siegel, I. M.: Rhodop-

sin and visual thresholds in congenital nightblindness. J. Physiol. 186:103, 1966.
6. Carroll, F. D., and Haig, C.: Congenital stationary nightblindness without ophthalmoscopic or other abnormalities. Trans. Am. Ophthalmol. Soc. 50:193, 1952.
7. Riggs, L. A.: Electroretinography in cases of nightblindness. Part II. Am. J. Ophthalmol. 38:70, 1954.
8. François, J., Verriest, G., DeRouck, A., and DeJean, C.: Les fonctions visuelles dans l'héméralopie essentielle nougarienne. Ophthalmologica 132:244, 1956.
9. François, J., Verriest, G., and De Rouck, A.: A new pedigree of idiopathic congenital night blindness. Am. J. Ophthalmol. 59:621, 1965.
10. Ripps, H., and Weale, R. A.: Flash bleaching of rhodopsin in the human retina. J. Physiol. 200:151, 1969.
11. Ripps, H., Carr, R. E., Siegel, I. M., and Greenstein, V. C.: Functional abnormalities in vincristine-induced night blindness. Invest. Ophthalmol. 25:787, 1984.
12. Gouras, P., and MacKay, C. J.: Light-adapting the cone electroretinogram. Invest. Ophthalmol. 30:625, 1989.
13. Auerbach, E., Godel, V., and Rowe, H.: An electrophysiological and psychophysical study of two forms of congenital nightblindness. Invest. Ophthalmol. 8:332, 1969.
14. Schubert, G., and Bornschein, H.: Beitrag zurt Analyse des menschlichen Elektroretinogramms. Ophthalmologica 123:396, 1952.
15. Miyake, Y., Yagasaki, K., Horiguchi, M., Kawase, Y., and Kanda, T.: Congenital stationary night blindness with negative electroretinogram. Arch. Ophthalmol. 104:1013, 1986.
16. Carr, R. E., and Ripps, H.: Rhodopsin kinetics and rod adaptation in Oguchi's disease. Invest. Ophthalmol. 6:426, 1967.

OPHTHALMIC MINIATURE

"Publishers are always losing manuscripts. I think sometimes that's their main activity. But a scapegoat is always necessary, don't you agree? My only complaint is that she doesn't lose the ones I'd like to see lost. Contretemps, these, in what the good Bacon called *The Advancement of Learning*."

Umberto Eco, *Foucault's Pendulum*
New York, Harcourt Brace Jovanovitch, 1989, p. 73

Correlation of Visual Function and Retinal Leukocyte Velocity in Glaucoma

William E. Sponsel, M.D., Kathleen L. DePaul, M.S., and Paul L. Kaufman, M.D.

Twelve subjects with glaucoma or ocular hypertension underwent measurement of visual fields (Humphrey perimeter and the Henson CFS2000 perimeter), contrast sensitivity (Vistech wall charts), and perimacular leukocyte velocity (Oculix BFS-1000 blue field entoptic technique). Significant positive correlations were seen between asymmetry of visual function and asymmetry of retinal leukocyte velocity in the study population. The eye with the higher velocity of retinal leukocyte flow tended to have better visual function as measured by Humphrey mean deviation ($P < .05$), Henson Score ($P < .06$), and Vistech contrast sensitivity score at 6 cycles/degree ($P < .001$). An association of borderline significance was found between the asymmetries of intraocular pressure and retinal leukocyte velocity ($P = .06$). No significant intraocular pressure:visual field correlations were found on asymmetry analysis, although the inverse relationship between intraocular pressure and contrast sensitivity was significant ($P < .05$). Significant correlations were obtained between visual field scores derived from the Henson data and Humphrey parameters mean deviation ($P < .001$) and corrected pattern standard deviation ($P < .05$) on both asymmetry and single eye analysis.

GLAUCOMATOUS VISUAL LOSS is associated with compromise of ganglion cell function. This process is often associated with an increase in intraocular pressure, but the pathophysiologic relationship between intraocular pressure and visual function remains unclear. Only a minority of eyes with documented increased intraocular pressure actually develop clinically significant visual field loss over a five- to ten-year period.[1-6] Moreover, large-scale epidemiologic studies suggest that approximately one half of such visual defects detected de novo are found in concomitantly normotensive eyes.[6-13]

It has been suggested that glaucomatous visual field loss, in both hypertensive and normotensive eyes, might develop in association with vascular insufficiency to the optic nerve head or retinal ganglion cell axons.[14] Until recently, few means were available to estimate retinal hemodynamic changes in a clinical setting. Pulse-synchronized computer simulations of entoptically visualized leukocyte motion, developed by Riva and Petrig,[15] now allow for reproducible subjective measurements of perimacular leukocyte velocity and density. Recent studies have reaffirmed the likely source of the blue field entoptic phenomenon to be leukocytes flowing within the macular retinal microvasculature.[16] We studied the associations between leukocyte velocity, visual fields, contrast sensitivity, and intraocular pressure in patients with ocular hypertension or primary open-angle glaucoma.

Material and Methods

The subject population comprised five patients with ocular hypertension and normal disks and fields; three patients with ocular hypertension and suspicious disks or fields; and four primary open-angle glaucoma patients with unequivocal visual field loss and disk abnormalities. There were eight men and four women with an average age of 62 years (range, 27 to 75 years). All but one subject had a Snellen acuity of 20/30 or better in each eye and ≤1 line of difference between the two eyes. The remaining subject had a visual acuity of

Accepted for publication Sept. 22, 1989.

From the University of Wisconsin-Madison Department of Ophthalmology. This study was supported by a grant from Chibret International. Portions of this study were presented at the Noninvasive Assessment of the Visual System Topical Meeting of the Optical Society of America, Santa Fe, New Mexico, February 13, 1989, and at the annual meeting of the Association for Research in Vision and Ophthalmology, Sarasota, Florida, May 1, 1989.

Reprint requests to William E. Sponsel, M.D., Department of Ophthalmology, F4/3 CSC, University of Wisconsin-Madison, 600 Highland Ave., Madison, WI 53792.

R.E.: 20/25 and L.E.: 20/50, but equivalent working threshold values on Henson perimetry in both eyes.

Nine of the 12 subjects were receiving medical intraocular pressure lowering medication at each visit. In 25 of the 30 patient visits, the pharmacologic treatment status of both eyes was identical (Table 1).

All subjects had experience in perimetry, having had a minimum of two pairs of Humphrey visual fields before their entry into the study. Data for each testing modality were averaged from measurements obtained in the preceding year. Both study visits were averaged for six subjects who had been tested twice only. Three randomly selected visits were averaged for the remaining six subjects who had been seen three or more times. Visits averaged 2½ hours' duration.

Visual fields, contrast sensitivity, intraocular pressure, and retinal leukocyte velocity were measured at each visit. Mean values for visual function scores, intraocular pressure, and leukocyte velocity were compiled for each subject from two or three separate visits as outlined above. Visits were conducted at approximately three-month intervals. Correlations were determined for each pair of parameters studied using the right eye only (single eye analysis) and the difference between the right and left eyes (asymmetry analysis).

Perimetric techniques—Visual field examina-

TABLE 1
TREATMENT BY VISIT FOR 12 SUBJECTS

SUBJECT NO.	VISIT NO.	TREATMENT
1	1	Timolol 0.5% and dipivefrin 0.1% twice daily, both eyes
	2	Timolol 0.5% and dipivefrin 0.1% twice daily, both eyes; Ocusert-Pilo 40 once weekly, both eyes
	3	Timolol 0.5% and dipivefrin 0.1% twice daily, both eyes; Ocusert-Pilo 40 once weekly, both eyes
2	1	Timolol 0.5% twice daily, both eyes
	2	Timolol 0.5% twice daily, both eyes
	3	Timolol 0.5% twice daily, both eyes; pilocarpine 4% twice daily, R.E., four times daily, L.E.
3	1	Timolol 0.5% and dipivefrin 0.1% twice daily, both eyes
	2	Timolol 0.5% and dipivefrin 0.1% twice daily, both eyes
	3	Timolol 0.5% and dipivefrin 0.1% twice daily, both eyes
4	1	Timolol 0.5% twice daily, both eyes
	2	Timolol 0.5% twice daily, both eyes; dipivefrin 0.1% twice daily, R.E.
	3	Timolol 0.5% and dipivefrin 0.1% twice daily, both eyes
5	1	Dipivefrin 0.1% and betaxolol 0.5% twice daily, both eyes
	2	Dipivefrin 0.1% and betaxolol 0.5% twice daily, both eyes; pilocarpine 2% four times daily, R.E.
	3	Dipivefrin 0.1% and betaxolol 0.5% twice daily, both eyes; pilocarpine 2% four times daily, R.E.
6	1	Betaxolol 0.5% and dipivefrin 0.1% twice daily, both eyes; pilocarpine 4% at bedtime, both eyes; acetazolamide 500 mg once daily orally
	2	Timolol 0.5% twice daily, both eyes; acetazolamide 500 mg once daily orally
	3	Timolol 0.5% twice daily, both eyes; pilocarpine 4% at bedtime, both eyes; acetazolamide 500 mg once daily, orally
7	1	Betaxolol 0.5% twice daily, both eyes
	2	Betaxolol 0.5% twice daily, both eyes
8	1	Timolol 0.25% twice daily, both eyes
	2	Timolol 0.25% twice daily, both eyes
9	1	Timolol 0.25% twice daily, R.E.
	2	None
10	1	None
	2	None
11	1	None
	2	None
12	1	None
	2	None

tions were performed with both the Humphrey perimeter (30-2 program) and the Henson CFS2000 perimeter.[17] The Humphrey perimeter is a bowl perimeter using single, projected light stimuli; the 30-2 program is an automated full-threshold 30-degree examination that tests 72 points and requires 12 to 18 minutes per eye. The Henson perimeter, which is semiautomated, uses multiple light-emitting diode stimuli on a flat screen to test a 25-degree field of 132 points. Although the Henson tests a greater number of points, it requires only three to four minutes per eye to perform a suprathreshold examination. Midfield threshold was estimated using 24 stimulus locations at 10 to 15 degrees eccentricity. Using this midfield threshold value, the Henson estimates thresholds for each of the 132 stimulus locations, assuming a 0.33 log unit/degree decrease in retinal sensitivity from fixation to the periphery. Testing commences at 0.5 log units brighter than the estimated threshold at all 132 locations. Defect depth was quantified by testing at two additional incremental light intensities (0.8 and 1.2 log units) brighter than threshold.

In our analyses, we considered two parameters provided by the Humphrey statistical package (Statpac)[18]: the mean deviation (the weighted average deviation of the measured thresholds from that of an age-matched control population, which becomes more negative with depression of retinal sensitivity) and corrected pattern standard deviation (the deviation of the threshold pattern that cannot be attributed to short-term fluctuation, which becomes more positive with a higher degree of focal variation in retinal sensitivity).

The Henson CFS2000 scores used in this study were calculated using the following equation: Henson score $= 100 - 3x - 2y - z$ (where x = number of points missed at 1.2 level; y = number of points missed at 0.8 level; and z = number of points miss at 0.5 level). To detect global rather than focal loss, no cluster scoring algorithm was incorporated in this analysis.[19]

Estimation of perimacular leukocyte velocity—Retinal leukocyte velocity was subjectively measured using the Oculix BFS-1000. This system, similar to one described previously,[15] allows subjects to visualize their own retinal leukocyte movements by means of blue light entoptic illumination. The speed of mock-leukocyte images on a pulse-synchronized computer simulation (seen on a video monitor within 14 degrees of fixation) was subjectively matched to entoptically perceived leukocyte motion. A trained operator interacted with the subject, adjusting simulation speeds from randomized starting levels according to a fixed protocol, using verbal feedback. A set of five velocity readings was averaged to provide an estimate of retinal leukocyte velocity at each visit. The standard deviation was calculated for each set of five readings; the mean coefficient of variation of the velocity readings in this population was 14%.

Contrast sensitivity—Contrast sensitivity at five static spatial frequencies (1.5, 3, 6, 12, and 18 cycles/degree) was estimated using Vistech wall charts with a background luminance of 900 candelas/m^2. The system produces an integral score from 0 through 8 for each frequency, corresponding to a contrast range of 8 to 230, increasing by factors of 1.33 to 2.00. Scores for 3 and 6 cycles/degree, which have been inferred to be more sensitive to glaucoma-specific change,[20] were used in these analyses. Scores from each of two different charts were averaged for each eye at each visit.

Tonometry—Intraocular pressures were obtained by Goldmann applanation tonometry at the end of each visit. Subjects were specifically questioned about whether they had taken their medications as scheduled on each day of testing. Compliance was putatively positive on all visits.

Results

The linear correlations found on asymmetry analysis are summarized in Table 2. Positive correlations were seen between the asymmetry of retinal leukocyte velocity and the asymmetry of visual function, as measured by Humphrey mean deviation (Fig. 1, left, $P < .05$); Henson score ($P = .06$); and contrast sensitivity scores at 6 cycles/degree (Fig. 1, middle, $P < .001$) and 3 cycles/degree ($P < .01$). Thus, the eye with the higher rate of retinal leukocyte flow tended to have better visual function.

A negative association of borderline statistical significance was found between the asymmetries of intraocular pressure and retinal leukocyte velocity (Fig. 1, right, $P = .06$). Thus, the eye with the lower intraocular pressure tended to have the faster leukocyte velocity. No correlations were found between intraocular pressure and any of the visual field parameters or contrast sensitivity at 3 cycles/degree. The asymmetry of intraocular pressure did correlate

TABLE 2
CORRELATIONS BETWEEN THE ASYMMETRY (R.E.–L.E.) OF PARAMETERS*

	HUMPHREY CORRECTED PATTERN STANDARD DEVIATION	HENSON FIELD SCORE	INTRAOCULAR PRESSURE	CONTRAST SENSITIVITY SCORE (6 CYCLES/DEGREE)	RETINAL LEUKOCYTE VELOCITY
Humphrey mean deviation	r = .54 (P = .07)	r = .90 (P < .001)	NS	r = .58 (P < .05)	r = .63 (P < .05)
Humphrey corrected pattern standard deviation	—	r = .62 (P < .05)	NS	NS	NS
Henson field score	—	—	NS	r = .52 (P = .09)	r = .56 (P = .06)
Intraocular pressure	—	—	—	r = .59 (P < .05)	r = .57 (P = .06)
Contrast sensitivity score (6 cycles/degree)	—	—	—	—	r = .91 (P < .001)

*For each entry, the independent variable is at the left and the dependent variable at the top; N = 12 for each correlation; r = correlation coefficient; P is the probability that r = 0; NS indicates that P > .10.

significantly with the asymmetry of contrast sensitivity score at 6 cycles/degree (Fig. 2, left, P < .05), with the lower intraocular pressure associated with the higher contrast sensitivity score.

Figure 2, right, shows the asymmetry of mean deviation vs asymmetry of contrast sensitivity score at 6 cycles/degree (P < .05). Asymmetry of contrast sensitivity score at 3 cycles/degree also correlated significantly with mean deviation and Henson score asymmetries (P < .05 for each), with the better field score tending to correspond with the higher contrast sensitivity value.

Analyses were performed to determine the degree of association between Snellen acuity and the hemodynamic and visual function parameters. No significant correlation was observed between asymmetry of Snellen acuity and any of the contrast sensitivity or visual field scores (P > .10). There was an association of borderline significance between the asymmetries of Snellen acuity and leukocyte velocity (P = .06).

The only significant correlations found on single eye analysis were among the perimetric parameters. Significant correlations were found among all three visual field parameters: mean deviation vs corrected pattern standard deviation (P < .001), mean deviation vs Henson

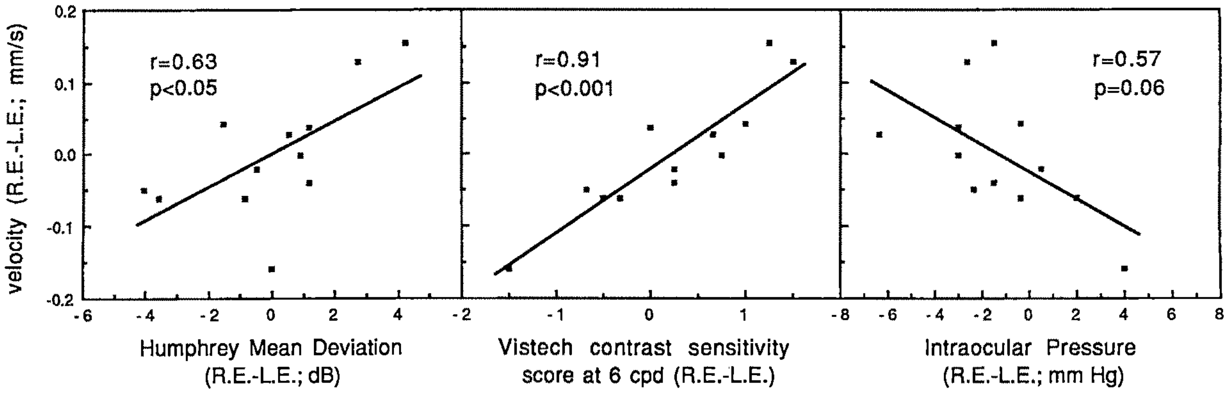


Fig. 1 (Sponsel, DePaul, and Kaufman). Asymmetry of retinal leukocyte velocity vs asymmetry of Humphrey mean deviation (left), Vistech contrast sensitivity score at 6 cycles/degree (middle), and intraocular pressure (right).

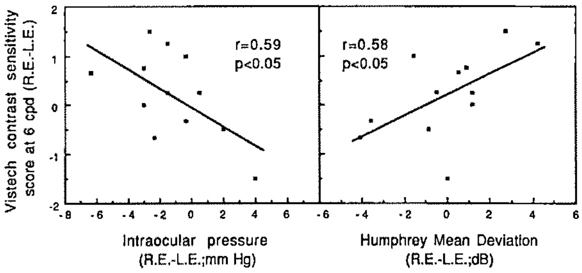


Fig. 2 (Sponsel, DePaul, and Kaufman). Asymmetry of Vistech contrast sensitivity score at 6 cycles/degree vs asymmetry of intraocular pressure (left), and Humphrey mean deviation (right).

score ($P < .001$), and corrected pattern standard deviation vs Henson score ($P < .01$). Significant correlations between Henson score and both Humphrey mean deviation ($P < .001$) and corrected pattern standard deviation ($P < .05$) were obtained on asymmetry analysis.

Discussion

Asymmetry analysis provides a means for neutralizing interindividual scatter in the evaluation of physiologic variables. Bilateral symmetry in the paired eyes of normal subjects is high for all the parameters tested in this study. Asymmetry of visual field defect scores tends to increase when glaucomatous change occurs in either or both eyes.[21] Asymmetry analysis disclosed associations of retinal leukocyte velocity with both visual field and contrast sensitivity scores, as well as a borderline correlation with intraocular pressure. The two perimeters produced concordant quantitative visual field data on the basis of both uniocular and asymmetry analysis.

Grunwald and associates[22] were the first to observe that retinal leukocyte velocity asymmetry accompanies qualitative visual field asymmetry. Of 49 glaucoma patients tested in their laboratory, 33 described a difference in baseline leukocyte speed between the eyes. Twenty-eight of those 33 patients (85%) were found to have slower leukocyte velocity in the eye with greater visual field loss. The 16 patients with symmetric baseline leukocyte velocity readings tended to be younger ($P < .001$), to have had disease of shorter duration ($P < .05$), and showed less difference between the eyes in maximal intraocular pressure levels ($P < .01$) than the 33 patients with asymmetric leukocyte velocity.

The association between asymmetric leukocyte velocity and visual function loss in glaucoma patients has been quantitatively confirmed in this study, with asymmetry of retinal leukocyte velocity correlating well with asymmetry of visual field scores. Even stronger associations were found between the asymmetries of retinal leukocyte velocity and contrast sensitivity, possibly because both measurements involve the macular region. Snellen visual acuity varied only marginally ($P = .06$) with leukocyte velocity and showed no significant statistical association with any of the visual function tests.

We cannot speculate whether the observed association between the asymmetries in retinal leukocyte velocity and visual function in these glaucoma patients is a cause or a consequence of ganglion cell degeneration. Intraocular pressure asymmetry was associated with hemodynamic and contrast sensitivity shifts, but not with perimetric differences, in this largely bilaterally symmetrically treated population. This study reaffirms the association between the physiologic status of the retinal vasculature and visual function in glaucoma, as others have also shown.[23-26] Clarification of the pathophysiologic relevance of such findings demands further study of both treated and untreated glaucomatous eyes.

References

1. Armaly, M.: Lessons to be learned from the Collaborative Glaucoma Study. Surv. Ophthalmol. 25:139, 1980.

2. Armaly, M. F., Krueger, D. E., Maunder, L. R., Becker, B., Hetherington, J., Kolker, A. E., Levene, R. Z., Maumenee, A. E., Pollack, I. P., and Shaffer, R. N.: Biostatistical analysis of the Collaborative Glaucoma Study. I. Summary report of the risk factors for glaucomatous visual field defects. Arch. Ophthalmol. 98:2163, 1980.

3. Bengtsson, B.: The prevalence of glaucoma. Br. J. Ophthalmol. 65:46, 1981.

4. Hollows, F. C., and Graham, P. A.: Intraocular pressure, glaucoma, and glaucoma suspects in a defined population. Br. J. Ophthalmol. 50:570, 1966.

5. Leibowitz, H. M., Krueger, D. E., Maunder, L. R., Milton, R. C., Kini, M. M., Kahn, H. A., Nickerson, R. J., Pool, J., Colton, T. L., Ganley, J. P., and Loewenstein, J. I.: The Framingham Eye Study monograph. Surv. Ophthalmol. 24(suppl):366, 1980.

6. Leske, M. C.: The epidemiology of open-angle

glaucoma. A review. Am. J. Epidemiol. 118:116, 1983.

7. Armaly, M. F.: The visual field defect and ocular pressure level in open angle glaucoma. Invest. Ophthalmol. 8:105, 1969.

8. Graham, P. A.: Epidemiology of simple glaucoma and ocular hypertension. Br. J. Ophthalmol. 56:223, 1972.

9. Linnér, E., and Stromberg, N.: Ocular hypertension. A five year study of the total population in a Swedish town, Skövde. In Leydhecker, W. (ed.): Glaucoma Symposium, Tutzing Castle. Basel, S. Karger, 1967, pp. 187–214.

10. Norskov, K.: Glaucoma screening. Parts I and II. Acta Ophthalmol. 48:401, 1970.

11. Perkins, E. S.: The Bedford Glaucoma Survey. I. Long-term follow-up of borderline cases. Br. J. Ophthalmol. 57:179, 1973.

12. Schappert-Kimmisjer, J.: A five-year follow-up of subjects with intraocular pressure of 22-30 mm Hg without anomalies of optic nerve and visual field typical for glaucoma at first investigation. Acta Ophthalmol. 162:289, 1971.

13. Schwartz, B.: Primary open-angle glaucoma. In Duane, T. D. (ed.): Clinical Ophthalmology, vol. 3. Philadelphia, Harper & Row, 1986, ch. 52, pp. 2–4.

14. Hayreh, S. S., Revie, I. H S., and Edwards, J.: Vasogenic origin of visual field defects and optic nerve changes in glaucoma. Br. J. Ophthalmol. 54:461, 1970.

15. Riva, C. E., and Petrig, B.: Blue field entoptic phenomenon and blood velocity in the retinal capillaries. J. Opt. Soc. Am. 70:1234, 1980.

16. Sinclair, S. H., Azar-Cavanagh, M., Soper, K. A., Tuma, R. F., and Mayrovitz, H. N.: Investigation of the source of the blue field entoptic phenomenon. Invest. Ophthalmol. Vis. Sci. 30:668, 1989.

17. Henson, D. B., and Bryson, H.: Clinical results with the Henson-Hamblin CFS2000. Doc. Ophthalmol. Proc. Ser. 49:233, 1987.

18. Heijl, A., Lindgren, G., and Olsson, J.: A package for the statistical analysis of visual fields. Doc. Ophthalmol. Proc. Ser. 49:153, 1987.

19. Henson, D., Hobley, A., Chauhan, B., Sponsel, W., and Dallas, N.: Importance of visual field score and asymmetry in the detection of glaucoma. Am. J. Optom. Physiol. Opt. 63:714, 1986.

20. Ross, J. E., Bron, A. J., and Clarice, D. D.: Contrast sensitivity and visual disability in chronic simple glaucoma. Br. J. Ophthalmol. 68:821, 1984.

21. Sponsel, W. E., Hobley, A., Henson, D. B., Chauhan, B. C., and Dallas, N. L.: Quantitative supra-threshold static perimetry. The value of field score and asymmetry analysis in the early detection of open-angle glaucoma. Doc. Ophthalmol. Proc. Ser. 49:217, 1987.

22. Grunwald, J. E., Riva, C. E., Stone, R. A., Keates, E. U., and Petrig, B. L.: Retinal autoregulation in open-angle glaucoma. Ophthalmology 91:1690, 1984.

23. Grehn, F., and Prost, M.: Function of retinal nerve fibers depends on perfusion pressure. Neurophysiologic investigations during acute intraocular pressure elevation. Invest. Ophthalmol. Vis. Sci. 24:347, 1983.

24. Schwoerer, J., Wu, D. C., Schwartz, B., and Banwatt, R. S.: Relative changes in vessel caliber with visual field loss in glaucoma patients measured by computerized image analysis. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1989, p. 429.

25. Jonas, J. B., Nguyen, X. N., and Naumann, G. O. H: Parapapillary retinal vessel diameter in normal and glaucoma eyes. Part I. Invest. Ophthalmol. Vis. Sci. 30:1599, 1989.

26. Jonas, J. B., and Naumann, G. O H.: Parapapillary retinal vessel diameter in normal and glaucoma eyes. Part II. Invest. Ophthalmol. Vis. Sci. 30:1604, 1989.

OPHTHALMIC MINIATURE

Another wash: A cent's worth of pure, refined white copperas dissolved in a pint of water, is also a good lotion; but label it poison, as it should never go near the mouth. Bathe the eyes with the mixture, either with the hands or a small piece of linen cloth, allowing some of the liquid to get under the lids.

Hugo Zieman and Mrs. F. L. Gillette, *The White House Cook Book*
New York, The Saalfield Publishing Company, 1907, p. 509

Contact B-Scan Echography in the Assessment of Optic Nerve Cupping

Deborah A. Darnley-Fisch, M.D., Sandra Frazier Byrne, J. Randall Hughes, B.S., Richard K. Parrish II, M.D., and William J. Feuer, M.S.

We determined the reliability of high-resolution contact B-scan echography for estimating the optic cup size in 56 eyes of 28 patients with glaucoma or ocular hypertension. Two trained observers independently evaluated horizontal and vertical cup/disk ratios in stereophotographs, and two skilled echographers independently estimated optic cup size in photoechograms in a masked fashion. The reliability of echographic interpretation varied (kappa 0.29 to 0.71), but it always exceeded that expected by chance alone, even for cups of 0.3 disk diameter or less. Subtly saucer-shaped cups (three of 50 eyes) and deep cups with intact neuroretinal rims (two of 50 eyes) were misinterpreted echographically. High-resolution contact B-scan echography may provide a useful and reliable estimate of the optic cup size in eyes with opaque media.

Previous publications have advocated axial B-scan echographic techniques to display the optic cup, but report that a cup/disk ratio of 0.6 is the minimal cup detectable.[1-4] This relative insensitivity has been ascribed to artifacts and resolution limits associated with less sensitive instrumentation as well as an axial sound beam passing through the lens.[1-4]

To display the optic cup echographically, the lamina cribrosa and rim of the cup must be exposed to a relatively perpendicular sound beam. The optic disk may be displayed with three B-scan orientations. In the axial view, the sound beam is directed through the lens perpendicular to the optic disk and posterior fundus. With this approach, however, it is often difficult to delineate the small and medium-sized cups, and the large, saucer-shaped cups are impossible to detect. With the longitudinal approach, the sound beam is directed more obliquely to the disk, and the cup is displayed at the periphery of the echogram (Fig. 1). We used a vertical transverse approach, with the probe placed temporal to the limbus to scan the optic cup vertically (Fig. 2). We compared the echographic interpretation of vertical cup dimensions with stereophotographic determination, which we defined as actual vertical cup size.

Accepted for publication Oct. 13, 1989.

From the Department of Ophthalmology, Bascom Palmer Eye Institute, University of Miami School of Medicine, Miami, Florida. This study was supported in part by Research to Prevent Blindness, Inc., New York, New York and Core Center Grant P30-EY-02180.

Reprint requests to Sandra Frazier Byrne, Bascom Palmer Eye Institute, P.O. Box 016880, Miami, FL 33101.

Subjects and Methods

We studied 28 patients with clear media bilaterally and known glaucoma or ocular hypertension in one or both eyes. The protocol and informed consent were approved by the University of Miami School of Medicine Subcommittee for the Use of Humans in Research before the inception of the study. Informed consent was obtained from each participant according to legal requirements. Pupillary dilation was achieved by instilling one drop of 2.5% phenylephrine and 1% tropicamide at five-minute intervals in each eye. If dilation was inadequate for fundus photography, the drops were reinstilled after 30 minutes. Color stereophotographs (×2), centered on the optic nerve, were taken by an experienced ophthalmic photographer with a Zeiss fundus camera and Fujichrome 100 film.

Each patient was examined in a masked fashion by one of the two echographers (S.F.B. and J.R.H.) using high-resolution contact B-scan echography with the vertical transverse approach. After the cup was detected, the probe was shifted slightly, if necessary, to center the cup in the echogram for optimal resolution. System sensitivity (gain) was initially adjusted

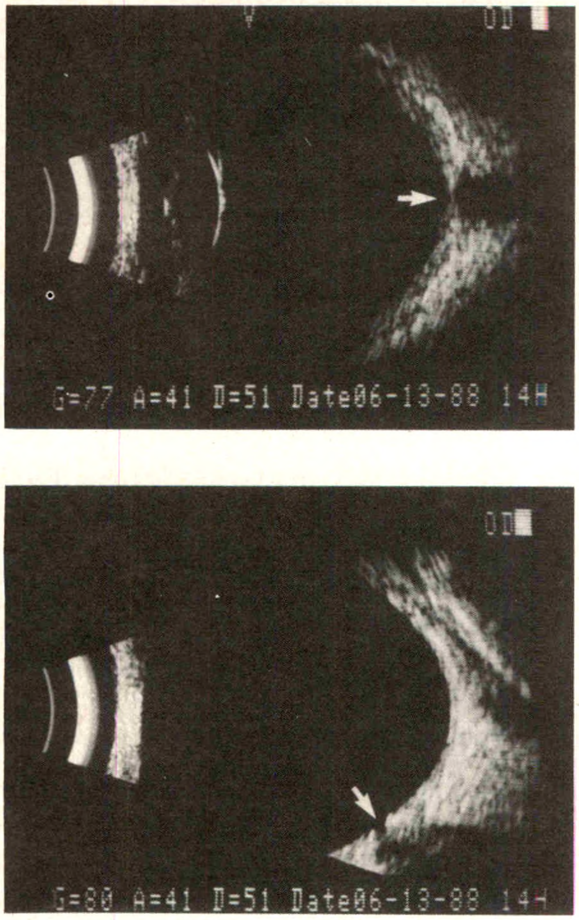
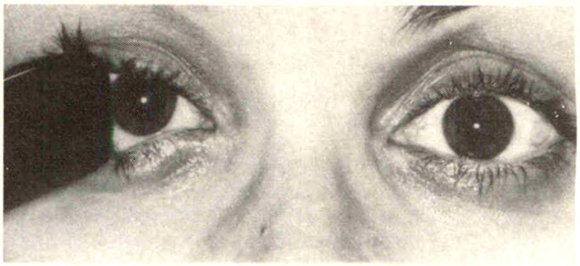


Fig. 1 (Darnley-Fisch and associates). Contact B-scan of a large optic cup. Top, Optic cup (arrow) poorly displayed in vertical axial profile. Bottom, Longitudinal view of the 3:00 o'clock meridian of the right eye demonstrates horizontal cross section of the optic cup (arrow) at the periphery of the echogram.



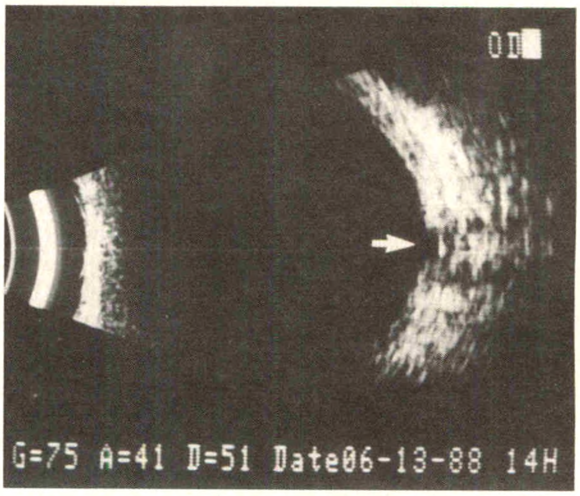


Fig. 2 (Darnley-Fisch and associates). Vertical transverse view of the same large cup shown in Figure 1. Top, B-scan probe placed temporally (marker aimed superiorly). Bottom, Well-centered and clearly demonstrated large vertical cup (arrow).

to a medium-high level and was then decreased until the rim and lamina cribrosa were delineated as clearly as possible. The sensitivity level used varied from patient to patient according to the configuration and size of the cup. After an excavation of maximal width and depth was displayed, the echogram was frozen and a Polaroid photoechogram was taken. The same technique was repeated on the fellow eye at a similar sensitivity setting for comparison. The two echographers subsequently evaluated the photoechograms independently. Each recorded cup size as small, medium, or large for each eye examined (Fig. 3).

Two trained stereophotograph observers (R.K.P. and D.A.D.-F.) independently viewed stereophotographic pairs of 35-mm transparencies to estimate the horizontal and vertical cup/disk ratio of each optic disk to the nearest one-tenth. A 2X stereoviewer was used. Estimations were made without aid of a linear scale. To correspond with the echographic evaluation, optic cups were categorized according to the vertical cup/disk ratio, that is, small (0.0 to 0.3), medium (0.4 to 0.6), or large (0.7 to 1.0).

Kappa[5] was used as a measure of interobserver agreement. Kappa ranges from 1.0 (when observers agree on the diagnosis in every case) to −1.0 (when observers disagree on the diagnosis in every case), and is zero when observers agree no more often than would be expected by chance alone. Kappa values were computed for each of the size categories. Because these three categories could be sensibly ordered, we also computed weighted kappa (Kw) values. In the calculation of weighted kappa values, cases with exact agreement are more heavily weighed than those that differ by one category. We computed weighted kappa values because the misinterpretation of a small for a large cup, or vice versa, is clinically a more important error than an error crossing only one category, and kappa regards all misinterpretations identically. We believe this is especially important in our category definitions, wherein a difference of 0.1

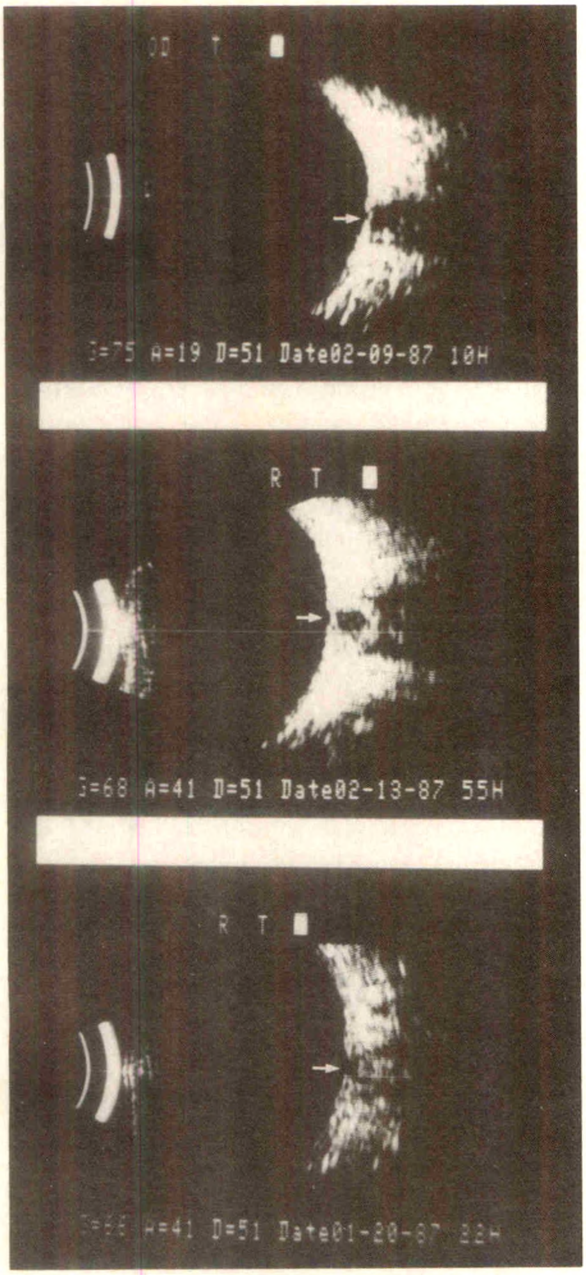


Fig. 3 (Darnley-Fisch and associates). Photoechographic examples of optic nerve cupping (arrow) with vertical transverse approach. Top, Cup/disk ratio = 0.1. Center, Cup/disk ratio = 0.4. Bottom, Cup/disk ratio > 0.9.

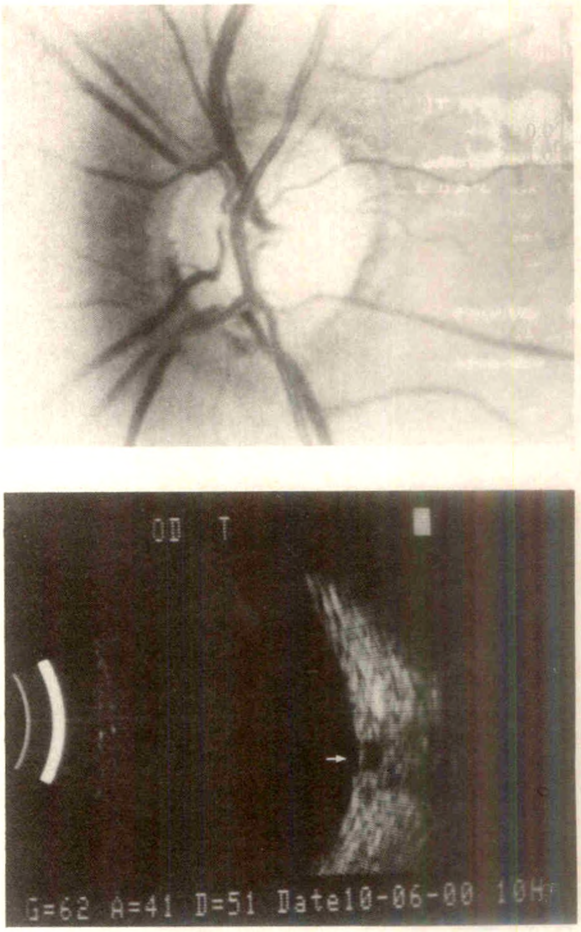


Fig. 4 (Darnley-Fisch and associates). Top, Photograph (× 2) of vertical optic cup described as 0.3 by stereophotograph Observer 1 and as 0.7 by stereophotograph Observer 2 and a third masked observer. Bottom, Central cup (arrow) described by both echographers as large.

in vertical dimension of the cup would result in reclassification. Ninety-five percent confidence intervals were computed for each kappa and weighted kappa value to indicate the numerical values between which chances are 95% that the actual kappa or weighted kappa falls. A Z-test[5] was computed for each kappa value to determine the significance of the difference from chance agreement for each echographic diagnosis.

We interpreted our kappa and weighted kappa results as suggested by Fleiss,[5] where a value of 0.75 or greater represents excellent agreement, and one less than 0.4 demonstrates poor agreement. Values between 0.4 and 0.75 indicate fair to good agreement. The results of both eyes of each subject were included in the study. If the extent of cupping in fellow eyes is not independent, significance levels could be artificially high and confidence intervals falsely small. For this reason, the analysis was conducted separately for left eyes and right eyes individually, and for all eyes combined. The results were found to be similar. For simplicity, we present only the combined analysis.

TABLE 1
COMPARISON OF READINGS BY STEREOPHOTOGRAPH OBSERVERS

		STEREOPHOTOGRAPH OBSERVER 1						
		SMALL	MEDIUM	LARGE	CLASSIFICATION	KAPPA	P VALUE* (KAPPA = 0)	95% CONFIDENCE INTERVAL OF KAPPA†
Stereophotograph observer 2	Small	10	0	0	Small	0.69	P < .001	(0.47,0.91)
	Medium	5	14	2	Medium	0.70	P < .001	(0.50,0.90)
	Large	1	0	18	Large	0.87	P < .001	(0.74,1.00)
					Weighted kappa	0.83	P < .001	(0.69,0.97)

*P value by Z-test.
†The standard error used to construct the 95% confidence interval limits is different than that used to test the null hypothesis of kappa being different than zero.

Results

Fifty of 56 eyes were well represented by both stereophotographs and photoechograms. Four stereophotographic pairs and two photoechograms were poorly focused and were therefore excluded from final review. The observations of stereophotograph observers are compared in Table 1. Both observers agreed in the categorization of 42 of 50 optic cups as small, medium, or large. Five of the eight eyes in dispute involved a difference in vertical cup estimation of one-tenth. Four of these occurred at the 0.3 to 0.4 border. One optic cup was described as 0.3 by one observer and 0.7 by the other (Fig. 4). A third masked observer described this cup as 0.7 using the same stereoviewing technique described in the previous section. Because this patient had substantial visual field loss compatible with moderately advanced cupping, the reading of 0.3 was judged to be a stereophotographic misinterpretation, but was not removed from the final data. Therefore, both echographers, who also interpreted this cup as large, were judged to be in error when compared with the stereophotograph observer.

The two skilled echographers agreed on cup size assessment in 36 of 50 photoechograms (Table 2). One optic nerve with a large and shallow cup was the source of disagreement (Fig. 5). One echographer properly identified the subtle but broad excavation in the photoechogram, and the other interpreted the cup as small. The kappa value ranged from 0.41 to 0.79, with a weighted kappa value of 0.75, and represented excellent agreement.

Comparison of individual stereophotograph and photoechogram readings is shown in Tables 3 through 6. Kappa values for each category and weighted kappa values for overall interobserver agreement are listed, with corresponding 95% confidence intervals and P values (Z-test[5]). Weighted kappa values ranged from 0.49 to 0.63. Pooling the estimates of agreement from all stereophotograph-photoechogram pairs yielded a combined weighted kappa value of 0.55 indicating fair to good agreement, but as is evident from the P values

TABLE 2
COMPARISON OF READINGS BY ECHOGRAPHERS

		ECHOGRAPHER 1						
		SMALL	MEDIUM	LARGE	CLASSIFICATION	KAPPA	P VALUE* (KAPPA = 0)	95% CONFIDENCE INTERVAL OF KAPPA†
Echographer 2	Small	9	8	1	Small	0.52	P < .001	(0.28,0.7)
	Medium	1	10	4	Medium	0.41	P < .005	(0.15,0.68)
	Large	0	0	17	Large	0.79	P < .001	(0.62,0.96)
					Weighted kappa	0.75	P < .001	(0.61,0.89)

*P value by Z-test.
†The standard error used to construct the 95% confidence interval limits is different than that used to test the null hypothesis of kappa being different than zero.

TABLE 3
COMPARISON OF READINGS BY STEREOPHOTOGRAPH OBSERVER 1 AND ECHOGRAPHER 1

		ECHOGRAPHER 1						
		SMALL	MEDIUM	LARGE	CLASSIFICATION	KAPPA	P VALUE* (KAPPA = 0)	95% CONFIDENCE INTERVAL OF KAPPA†
Stereophotograph observer 1	Small	6	7	3	Small	0.29	P < .05	(0.01,0.57)
	Medium	2	9	3	Medium	0.36	P < .01	(0.09,0.63)
	Large	2	2	16	Large	0.59	P < .001	(0.36,0.82)
					Weighted kappa	0.49	P < .001	(0.25,0.72)

*P value by Z-test.
†The standard error used to construct the 95% confidence interval limits is different than that used to test the null hypothesis of kappa being different than zero.

for Tables 3 through 6, interobserver agreement is significantly different from chance for the medium and small cups as well as for large cups.

Five optic disks were misinterpreted significantly by one or both echographers. One patient with advanced glaucoma had bilateral large, shallow optic cups, both of which were interpreted as small by one echographer (Fig. 5). The other echographer recognized subtle excavations and described the right cup as large and the left as medium. The third misdiagnosed cup was also saucer-shaped, and this pale, shallowly cupped, nearly totally excavated disk was interpreted as small by both echographers. Two deeply, well-demarcated optic cups with intact neuroretinal rim tissue that demonstrated prominent excavation photoechographically were interpreted by both echographers as large. The stereophotograph observers judged one vertical cup as medium and the other as small, resulting in a major misinterpretation for each echographer. One vertical optic cup was described as 0.3 by one stereophotograph observer and large by one echographer and resulted in a major echographic misinterpretation.

Discussion

Our data demonstrate that skilled echographers using high-resolution contact B-scan with a vertical transverse approach may properly define cups as small, medium, or large with fairly good accuracy. Generally, there was greater agreement in the identification of large cups, as was found also by Tielsch and associates[6] in a recent clinical and photographic study. Nevertheless, the echographers accurately interpreted even small and medium cups more frequently than could be expected by chance alone. The echographic description of shallow, saucer-shaped cups and congenitally large cups with intact neuroretinal rims is less reliable.[7,8]

Problems in identifying the subtle saucer-shaped cup echographically do not appear to be imminently solvable; even with subsequent informed review of the three misinterpreted shallow cups, the echographers were able to identify only probable cups. Both echographers stated that the shallow cups shown in Figure 5

TABLE 4
COMPARISON OF READINGS BY STEREOPHOTOGRAPH OBSERVER 1 AND ECHOGRAPHER 2

		ECHOGRAPHER 2						
		SMALL	MEDIUM	LARGE	CLASSIFICATION	KAPPA	P VALUE* (KAPPA = 0)	95% CONFIDENCE INTERVAL OF KAPPA†
Stereophotograph observer 1	Small	12	2	2	Small	0.56	P < .001	(0.31,0.80)
	Medium	2	9	3	Medium	0.47	P < .001	(0.20,0.73)
	Large	4	4	12	Large	0.44	P < .005	(0.19,0.70)
					Weighted kappa	0.51	P < .001	(0.26,0.75)

*P value by Z-test.
†The standard error used to construct the 95% confidence interval limits is different than that used to test the null hypothesis of kappa being different than zero.

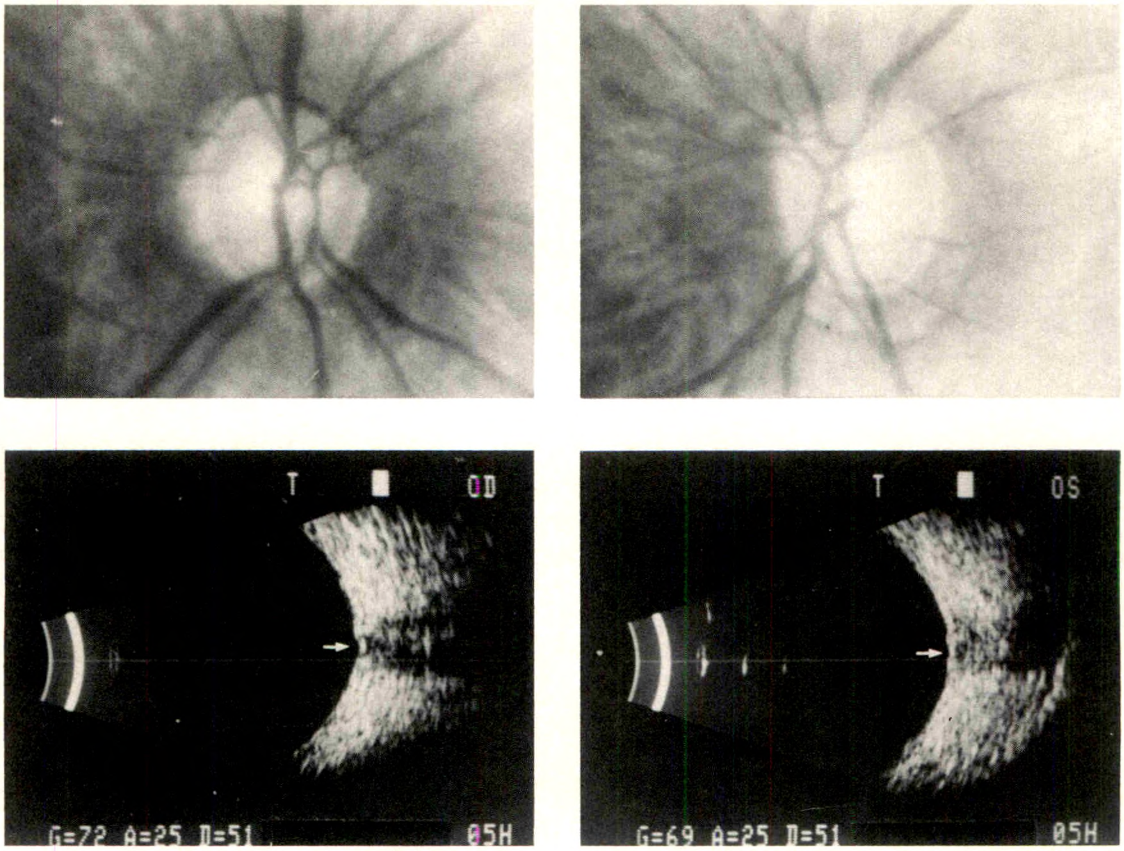


Fig. 5 (Darnley-Fisch and associates). Optic disks and corresponding photoechograms resulting in two major errors for one echographer. Top left, Right eye, and top right, left eye, were judged small by one echographer and large by both stereophotograph observers. Bottom left, Echogram of the right eye was the source of disagreement between echographers. Arrow indicates subtle echographic excavations.

would be interpreted as medium or large in the right eye but medium at most in the left eye in future examinations. Perception of these subtle excavations, however, might be heightened if clinical information about the patient were presented before echographic examination. An afferent pupillary defect, history of angle closure attack, intraocular inflammation, peripheral anterior synechiae, or intraocular pressure asymmetry might alert the echographer to this possibility.

Because the technique used in this study estimates the optic cup without knowledge of the surface area of the disk, variations in optic disk anatomy, as in the case of deep, congenital, physiologic cups, may result in erroneous echo-

TABLE 5

COMPARISON OF READINGS BY STEREOPHOTOGRAPH OBSERVER 2 AND ECHOGRAPHER 1

		ECHOGRAPHER 1						
		SMALL	MEDIUM	LARGE	CLASSIFICATION	KAPPA	P VALUE* (KAPPA = 0)	95% CONFIDENCE INTERVAL OF KAPPA†
Stereophotograph observer 2	Small	5	4	1	Small	0.38	P < .01	(0.06,0.69)
	Medium	4	13	4	Medium	0.46	P < .005	(0.21,0.71)
	Large	1	1	17	Large	0.71	P < .001	(0.52,0.91)
					Weighted kappa	0.63	P < .001	(0.43,0.83)

*P value by Z-test.

†The standard error used to construct the 95% confidence interval limits is different than that used to test the null hypothesis of kappa being different than zero.

TABLE 6
COMPARISON OF READINGS BY STEREOPHOTOGRAPH OBSERVER 2 AND ECHOGRAPHER 2

		ECHOGRAPHER 2						
		SMALL	MEDIUM	LARGE	CLASSIFICATION	KAPPA	P VALUE* (KAPPA = 0)	95% CONFIDENCE INTERVAL OF KAPPA†
Stereophotograph observer 2	Small	9	0	1	Small	0.52	P < .001	(0.28,0.6)
	Medium	6	12	3	Medium	0.49	P < .001	(0.24,0.73)
	Large	3	3	13	Large	0.57	P < .001	(0.33,0.80)
					Weighted kappa	0.56	P < .001	(0.34,0.79)

*P value by Z-test.
†The standard error used to construct the 95% confidence interval limits is different than that used to test the null hypothesis of kappa being different than zero.

graphic interpretations.[6,7] A congenitally large optic cup with an intact neuroretinal rim, however, could be accurately identified if the fellow disk were examined ophthalmoscopically and photoechographic excavations were symmetric.

Although this study suggests that echography alone is fairly accurate in establishing optic cup size, reliability may be improved by comparing the results with those of the fellow eye when its cup is ophthalmoscopically visible. The fellow optic cup may be used as a reference point to minimize the normal variations in disk size among patients.

We examined eyes with clear media in this study, in which the acoustic view of the optic disk was not attenuated by vitreal or preretinal disease, or both. These conditions, especially when membranes insert into the disk, would likely impair the echographic assessment of optic cup size in eyes with opaque media in which the nerve cannot be visualized.

Although, as recent studies describe, the neuroretinal rim area is more indicative of optic nerve integrity, this assessment is not possible in the eye with opaque media.[9-13] We suggest our technique as an adjunct in the preoperative evaluation of the eye with opaque media rather than as a replacement for established clinical signs, such as an afferent pupillary defect or absence of entoptic phenomena.

References

1. Skalka, H. W.: Ultrasonography of the optic nerve. In Smith, J. L. (ed.): Neuro-ophthalmology Update. New York, Masson Publishers USA, 1977, pp. 119–130.
2. ———: Ultrasonography of the optic nerve. Neuro-ophthalmol. 1:261, 1981.
3. Ossoinig, K. C.: Standardized echography. Basic principles, clinical applications, and results. Int. Ophthalmol. Clin. 19:127, 1979.
4. Cohen, J. S., Stone, R. D., Hetherington, J., Jr., and Bullock, J.: Glaucomatous cupping of the optic disc by ultrasonography. Am. J. Ophthalmol. 82:24, 1976.
5. Fleiss, J. L.: Statistical Methods for Rates and Proportions, ed. 2. New York, John Wiley and Sons, 1981, pp. 212–224.
6. Tielsch, J. M., Katz, J., Quigley, H. A., Miller, N. R., and Sommer, A.: Intraobserver and interobserver agreement in measurement of optic disc characteristics. Ophthalmology 95:350, 1988.
7. Bengtsson, B.: The variation and covariation of cup and disc diameters. Acta Ophthalmol. 54:804, 1976.
8. Teal, P. K., Morin, J. D., and McCulloch, C.: Assessment of the normal disc. Trans. Am. Ophthalmol. Soc. 70:164, 1972.
9. Airaksinen, P. J., Drance, S. M., and Schulzer, M.: Neuroretinal rim area in early glaucoma. Am. J. Ophthalmol. 99:1, 1985.
10. Britton, R. J., Drance, S. M., Schulzer, M., Douglas, G. R., and Mawson, D. K.: The area of the neuroretinal rim of the optic nerve in normal eyes. Am. J. Ophthalmol. 103:497, 1987.
11. Juvala, P. A., Airaksinen, P. J., Alanko, H. I., Tuulonen, A. E., and Valkonen, R. T.: Change in rim area of the optic nerve in ocular hypertensives and patients with glaucoma. Chibret Int. J. Ophthalmol. 5:36, 1987.
12. Mikelberg, F. S., Airaksinen, P. J., Douglas, G. R., Schulzer, M., and Wijsman, K.: The correlation between optic disk topography measured by the video-ophthalmograph (Rodenstock analyzer) and clinical measurement. Am. J. Ophthalmol. 100:417, 1985.
13. Mikelberg, F. S., Douglas, G. R., Schulzer, M., Airaksinen, P. J., Wijsman, K., and Mawson, D.: The correlation between cup-disk ratio, neuroretinal rim area, and optic disk area measured by the video-ophthalmograph (Rodenstock analyzer) and clinical measurement. Am. J. Ophthalmol. 101:7, 1986.

Intraocular Pressure Measurement With the Tono-Pen Through Soft Contact Lenses

William C. Panek, M.D., William A. Boothe, M.D., David A. Lee, M.D., Eva Zemplenyi, M.D., and Thomas H. Pettit, M.D.

We evaluated a miniaturized digital and electronic tonometer, the Tono-Pen, for accuracy of intraocular pressure measurement in the presence of a contact lens. In the manometric study, the Tono-Pen was used to measure a known intraocular pressure, ranging from 10 mm Hg to 60 mm Hg in a cadaver eye over soft contact lenses with different powers and a plano-T bandage lens. There was significant bias in pressure measurement over all contact lenses except for the plano-T, which had no bias at any level. In the clinical study, the intraocular pressures of 40 eyes in 20 normal patients were measured with and without a plano-T contact lens in place. Analysis of variance showed no significant interactive effect between the right and left eyes, with or without the lens. There was no significant difference in the Tono-Pen measurement of intraocular pressure over a plano-T contact lens compared with no lens.

MEASUREMENT OF INTRAOCULAR PRESSURE may, for many reasons, be necessary in patients wearing soft contact lenses. Patients with corneal disease often require therapeutic contact lenses that are essential to re-epithelialization and that must remain in place for extended periods of time.[1] In certain cases, such as after penetrating keratoplasty where the risk of secondary glaucoma is high[2] and where the use of a therapeutic contact lens is often necessary, the clinician must measure intraocular pressure with the contact lens in position or risk removing the lens earlier than desired.

Studies have shown that accurate measurements of the intraocular pressure can be made over therapeutic contact lenses with the Mackay-Marg tonometer[3] and the pneumatonometer.[4,5] The Tono-Pen, a hand-held tonometer that is similar in design to the Mackay-Marg tonometer,[6-8] has been previously described and shown to be accurate in measuring intraocular pressures in the normal eye[9,10] and in eyes with corneal disease.[11]

To assess the accuracy and reproducibility of the Tono-Pen in measuring intraocular pressure through a soft contact lens, we used the Tono-Pen to measure intraocular pressure over contact lenses and compared these values with readings made on the same eye without the lens in place.

Material and Methods

In the manometric study, a previously reported technique using a cannulated cadaver eye continuously monitored by a Grass Model 7B Polygraph was used to establish a known intraocular pressure.[9] Using the Tono-Pen, five measurements of the pressure were taken, with and without contact lenses in place, at transducer pressure increments of 10 mm Hg, ranging from 10 mm Hg to 60 mm Hg. The contact lenses used were Optech +2.00, +4.00, +6.00, +8.00, −10.00, and −12.00 diopters (water content, 55%) and Bausch and Lomb plano-T (water content, 38.6%).

In the clinical study, 20 patients (40 eyes) with normal corneas underwent measurement of intraocular pressure using the Tono-Pen. Measurements were taken initially in the right

Accepted for publication Oct. 24, 1989.

From the Jules Stein Eye Institute and Department of Ophthalmology, UCLA School of Medicine, Los Angeles, California. Dr. Panek was an Abe Meyer Fellow and Dr. Boothe was a Frances Howard Goldwyn Fellow. This study was supported by National Institutes of Health grant EY07701, Research to Prevent Blindness, Inc., Lucille Ellis Simon Glaucoma Research Fund, and the Karl Kirchgessner Foundation.

Reprint requests to William C. Panek, M.D., Jules Stein Eye Institute, UCLA School of Medicine, Center for the Health Sciences, Los Angeles, CA 90024-1771.

eye in the presence of a plano-T contact lens. The contact lens was then removed and the measurement repeated. The process was reversed for the left eye, with the measurement without the contact lens being made first and the measurement with the contact lens being made second. Both right and left eyes were measured five times in rapid succession, both with and without the contact lens.

Statistical analysis of the data in the manometric study was performed by analysis of variance and Gabriel's method of multiple comparison.[12] To compare eyes and the effect of the plano-T lens on intraocular pressure measurements in the clinical study, a two-way repeated measures analysis of variance was performed. A significance level equal to or less than .05 was considered statistically significant.

Results

Measurement of intraocular pressure with the Tono-Pen was not significantly altered by the presence of a plano-T lens in either the manometric or the clinical study.

In the manometric study, analysis of variance showed that differences in the various soft contact lenses and their effects on measurement of the known transducer intraocular pressure was highly variable and depended on the transducer setting. Bias was defined as measured intraocular pressure minus transducer setting. No consistent pattern of bias on Tono-Pen measurement of transducer pressure could be elicited on the basis of contact lens power. At each intraocular pressure level, the plano-T lens had the smallest bias for all levels less than 50 mm Hg (Table) (Figure). The bias of the measurements over the plano-T lens was not significant at any setting, coming close to significance ($P = .06$) only at the 50-mm Hg setting. Significant bias was present at all transducer settings with all of the other tested contact lenses.

In the clinical study, there was a mean $\pm$ S.D. ($N = 20$) intraocular pressure reading in the right eye of 17.19 ± 4.81 mm Hg with the plano-T contact lens, and a pressure of 17.09 ± 4.92 mm Hg without the lens. In the left eye, the measurement with the lens was 17.48 ± 4.93 mm Hg, and without the lens it was 16.77 ± 4.94 mm Hg. To compare eyes and the effect of the plano-T lens on intraocular pressure measurement, a two-way repeated measures analysis of variance was performed on the data. With this technique, no significant interactive effect was detected in either the right or left eye. Right and left eyes of a subject were thus averaged to measure contact lens effect. No significant difference was detected in measuring intraocular pressure with the Tono-Pen over a plano-T lens compared with no lens. There was an 82% chance of detecting a pressure difference of 1 mm with the sample size of 20 patients in the clinical study.

Discussion

In the manometric study, the Tono-Pen accurately assessed the intraocular pressure in a cadaver eye in the presence of a plano-T contact lens. This measurement controlled for transient fluctuations in intraocular pressure. As reported previously,[9] the cadaver eye model may produce problems with corneal surface irregularity and edema. The Tono-Pen, however, has been shown to yield valid readings in patients with irregular diseased corneas[11] and, therefore, may not be greatly affected by that variable.

Measurement of intraocular pressure over the other tested contact lenses was highly variable and unreliable. Krieglstein and associates,[4] using pneumatonometry, found that inaccuracy occurred with increased central thickness of the contact lens. McMonnies[13] believed that a central contact lens thickness of less than 0.15 mm was necessary for accurate readings. In this study, readings over both high-plus (thicker) and high-minus (thinner) contact lenses yielded poor results. The plano-T lens with a center thickness of 0.21 mm yielded the only reliable readings in our model.

In the clinical study, the Tono-Pen also reliably measured intraocular pressure in the presence of a plano-T contact lens. An attempt to control confounding variables such as pulse, respirations, and vascular influences was made by serially repeating measurements and reversing the contact lens sequence for each fellow eye. No significant differences could be seen between eyes, with or without contact lens, which supports the results of the laboratory study.

The accuracy of the Tono-Pen has been demonstrated in several clinical trials[9-11] in both normal[9,10] and diseased irregular corneas.[11] Other studies have shown that the Mackay-Marg tonometer and the pneumatonometer[4,5] are useful in measuring intraocular pressure

TABLE
STATISTICS COMPARING TRANSDUCER INTRAOCULAR PRESSURE READINGS WITH TONO-PEN INTRAOCULAR PRESSURE READINGS OVER DIFFERENT TYPES OF CONTACT LENSES

TRANSDUCER INTRAOCULAR PRESSURE (MM HG)	CONTACT LENS	AVERAGE INTRAOCULAR PRESSURE (MM HG)	MINIMUM INTRAOCULAR PRESSURE (MM HG)	MAXIMUM INTRAOCULAR PRESSURE (MM HG)	S.D.	AVERAGE BIAS
10	None	12.2	12	13	0.45	2.2
20	None	20.2	20	21	0.45	0.2
30	None	24.2	20	32	5.50	−5.8
40	None	41.8	40	44	1.79	1.8
50	None	50.6	46	55	3.65	0.6
60	None	57.2	53	60	2.59	−2.8
10	+2.00	12.0	11	14	1.22	2.0
20	+2.00	24.8	24	25	0.45	4.8
30	+2.00	32.8	31	36	1.92	2.8
40	+2.00	39.4	38	41	1.14	−0.6
50	+2.00	52.0	51	53	0.71	2.0
60	+2.00	60.4	60	61	0.55	0.4
10	+4.00	15.2	13	17	1.64	5.2
20	+4.00	22.6	21	25	1.52	2.6
30	+4.00	31.2	30	32	0.84	1.2
40	+4.00	41.8	40	43	1.30	1.8
50	+4.00	51.0	49	54	1.87	1.0
60	+4.00	61.0	60	63	1.41	1.0
10	+6.00	12.6	11	16	2.07	2.6
20	+6.00	26.6	25	30	2.30	6.6
30	+6.00	35.0	34	36	1.00	5.0
40	+6.00	45.2	43	47	1.48	5.2
50	+6.00	57.2	54	64	3.96	7.2
60	+6.00	61.0	55	64	3.54	1.0
10	+8.00	19.0	16	23	2.65	9.0
20	+8.00	31.6	28	34	2.51	11.6
30	+8.00	35.8	33	37	1.64	5.8
40	+8.00	45.8	45	48	1.30	5.8
50	+8.00	52.8	51	54	1.10	2.8
60	+8.00	63.2	61	66	1.79	3.2
10	−10.00	15.6	14	17	1.34	5.6
20	−10.00	20.6	17	26	3.78	0.6
30	−10.00	36.4	30	42	4.39	6.4
40	−10.00	48.4	44	56	4.56	8.4
50	−10.00	44.6	39	54	6.66	−5.4
10	−12.00	12.4	12	13	0.55	2.4
20	−12.00	19.8	19	21	0.87	−0.2
30	−12.00	28.6	28	30	0.89	−1.4
40	−12.00	36.2	35	37	0.84	−3.8
50	−12.00	43.0	41	47	2.35	−7.0
60	−12.00	49.0	47	51	1.87	−11.0
10	Plano T	10.8	10	12	0.84	0.8
20	Plano T	20.2	19	21	0.84	0.2
30	Plano T	30.4	29	33	1.95	0.4
40	Plano T	39.8	37	42	1.92	−0.2
50	Plano T	52.2	49	54	1.92	2.2
60	Plano T	58.2	56	63	2.78	−1.8

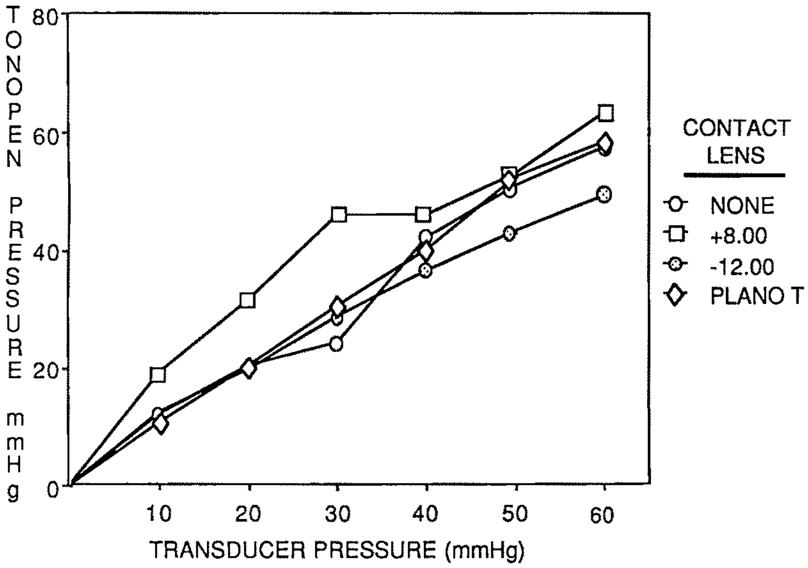


Figure (Panek and associates). Statistics of intraocular pressure measurements in a cadaver eye with the Tono-Pen in the presence of no contact lens, a plano-T contact lens, a +8.00 Optech soft contact lens, and a −12.00 Optech soft contact lens.

over a contact lens. This study indicates that the Tono-Pen may also be reliable in this setting. In patients wearing bandage soft contact lenses, intraocular pressure can be accurately and reliably measured without disturbing the lens and the underlying corneal epithelium.

References

1. Gassett, A. R., and Lobol, L.: Simplified soft contact lens treatment in corneal diseases. Ann. Ophthalmol. 9:843, 1977.

2. Irvine, A. R., and Kaufman, H. E.: Intraocular pressure following penetrating keratoplasty. Am. J. Ophthalmol. 68:835, 1969.

3. Meyer, R. F., Stanifer, R. M., and Bobb, K. C.: Mackay-Marg tonometry over therapeutic soft contact lenses. Am. J. Ophthalmol. 86:19, 1978.

4. Krieglstein, G. K., Waller, W. K., Reimers, H., and Langham, M. E.: Augeninnendruckmessung auf weichen Kontactlinsen. Graefes Arch. Clin. Exp. Ophthalmol. 199:223, 1976.

5. Rubenstein, J. B., and Deutsch, T. A.: Pneumatonometry through bandage contact lenses. Arch. Ophthalmol. 103:1660, 1985.

6. Mackay, R. S., Marg, E., and Oechsli, R.: Automatic tonometer with exact theory and various biological applications. Science 131:1668, 1960.

7. Mackay, R. S., and Marg, E.: Fast, automatic, electronic tonometers based on an exact theory. Acta Ophthalmol. 37:495, 1959.

8. Mackay, R. S., Marg, E., and Oechsli, R.: Evaluation of the basic validity and clinical usefulness of the Mackay-Marg tonometer. Invest. Ophthalmol. Vis. Sci. 1:78, 1962.

9. Boothe, W. A., Lee, D. A., Panek, W. C., and Pettit, T. H.: The Tono-Pen. A manometric and clinical study. Arch. Ophthalmol. 106:1214, 1988.

10. Minckler, D. S., Baerveldt, G., Heuer, D. K., Quillen-Thomas, B., Walonker, A. F., and Weiner, J.: Clinical evaluation of the Oculab Tono-Pen. Am. J. Ophthalmol. 104:168, 1987.

11. Rootman, D. S., Insler, M. S., Thompson, H. W., Parelman, J., Poland, D., and Unterman, S. R.: Accuracy and precision of the Tono-Pen in measuring intraocular pressure after keratoplasty and epikeratophakia and in scarred corneas. Arch. Ophthalmol. 106:1697, 1988.

12. Gabriel, K. R.: A simple method of multiple comparison of means. J. Am. Stat. Assoc. 73:724, 1978.

13. McMonnies, C. W.: Non-contact tonometry through soft contact lenses. Am. J. Optom. Physiol. Opt. 63:948, 1986.

Complications of Malpositioned Jones Tubes

George B. Bartley, M.D., and Ray O. Gustafson, M.D.

A Jones tube is an effective lacrimal drainage bypass device often associated with postoperative problems. Unsuspected migration of the tube may cause signs and symptoms that are not immediately identified with the prosthesis. Malposition of Jones tubes in three patients resulted in the following complications. The first patient had persistent episcleritis and atypical facial pain and numbness caused by migration of the tube against the globe and into the nasal septum. Bilateral tubes in the second patient were improperly oriented, causing severe scleral erosion and ulceration. The third patient's bilateral tubes migrated through the conjunctiva into the subcutaneous tissues and were manifested as lower eyelid inflammatory masses. Placement of a Jones tube requires long-term maintenance by the physician and the patient.

CONJUNCTIVODACRYOCYSTORHINOSTOMY (dacryocystorhinostomy with placement of a Pyrex glass Jones tube between the medial canthal angle and the nasal cavity) is an effective treatment for epiphora caused by canalicular atresia, severe canalicular stenosis, or loss of the orbicularis lacrimal pump.[1-3] Postoperative problems caused by Jones tubes usually result from malposition of the prosthesis. The tube should fit snugly in the medial canthal angle and be in contact with the lacrimal lake; the caruncle often must be excised to obtain correct positioning. The prosthesis should extend 2 mm beyond the lateral nasal wall, but it should not touch the nasal septum.[4]

The diagnosis and management of an improperly positioned tube are usually straightforward. Unsuspected migration of a Jones tube, however, may cause signs and symptoms that are not immediately identified with the prosthesis. Jones tube malposition was the cause of unusual complications in three patients.

Case Reports

Case 1

A 45-year-old woman, who 12 years previously had undergone bilateral conjunctivodacryocystorhinostomy with Jones tubes, had pain and redness of the right eye. The Jones tubes were noted to be properly positioned. Episcleritis was diagnosed and treated with oral aspirin and topical fluorometholone. Slight improvement was noted, but over the following month the patient began to have numbness and pain of the nose, right maxilla, and right ear. The patient was referred for evaluation of the persistent episcleritis and neurologic complaints.

The ophthalmic examination disclosed only sectoral episcleritis of the right eye that was presumed to be secondary to slight posterior and inferior displacement of the Jones tube. Neurologic consultation did not identify a specific cause for the "right trigeminal neuropathy." Review of a computed tomographic scan disclosed soft tissue swelling around the right Jones tube (Fig. 1). Intranasal examination disclosed deviation of the nasal septum to the right with abutment of the Jones tube against the septum. With the patient under general anesthesia, the right tube was replaced with a shorter tube with the aid of intraoperative nasal endoscopy. The patient's signs and symptoms immediately resolved, and the Jones tube has functioned without difficulty for over two years.

Case 2

A 38-year-old man underwent placement of bilateral Jones tubes by a plastic surgeon; the

Accepted for publication Oct. 18, 1989.

From the Departments of Ophthalmology (Dr. Bartley) and Otorhinolaryngology (Dr. Gustafson), Mayo Clinic and Mayo Foundation. This study was supported in part by an unrestricted grant from Research to Prevent Blindness, Inc.

Reprint requests to George B. Bartley, M.D., Department of Ophthalmology, Mayo Clinic, 200 First St. S.W., Rochester, MN 55905.

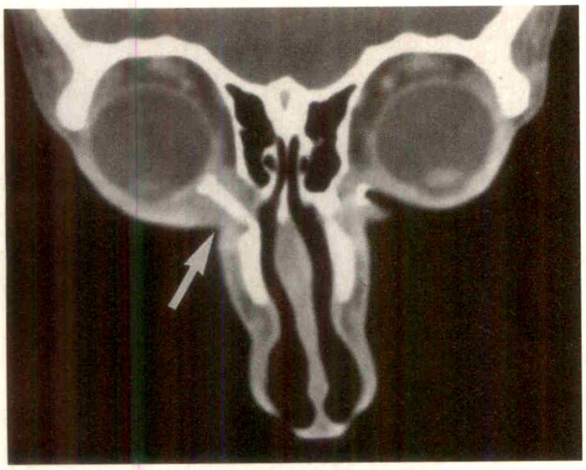


Fig. 1 (Bartley and Gustafson). Case 1. Computed tomographic scan from neurologic evaluation shows soft tissue swelling around right Jones tube (arrow).

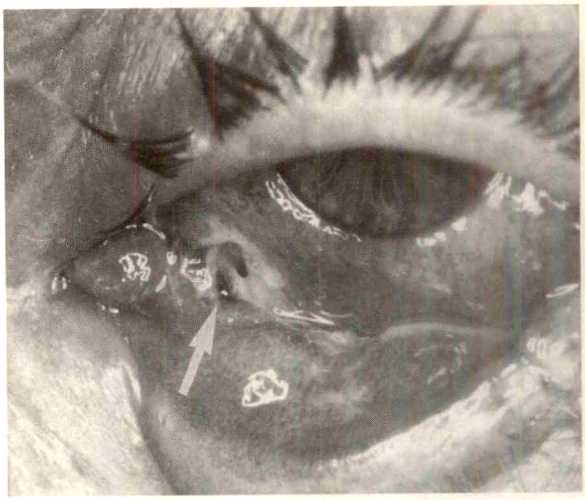


Fig. 2 (Bartley and Gustafson). Case 2. Scleral erosion and pressure necrosis from malpositioned Jones tube (arrow).

surgical report indicated that "the conjunctiva was sutured tightly around the tubes." An antibiotic-corticosteroid ointment was prescribed postoperatively. The left eye became painful two days after surgery, and prednisolone acetate 0.12% eyedrops were substituted for the ointment. Five days later, bilateral purulent conjunctivitis was diagnosed and the patient was referred for an ophthalmologic consultation.

The patient was in pain and the examination was difficult. A Jones tube was identified in each inferior fornix; each tube was directed upward at approximately a 30-degree angle rather than downward into the nose. Severe erosion of the sclera, greater in the left eye than the right eye, with copious purulent discharge was present (Fig. 2). The Jones tubes were removed and the patient was instructed to discontinue use of the prednisolone acetate. A large scleral ulcer persisted in the left eye for several days, but eventually both eyes healed without permanent ocular damage.

Case 3

A 66-year-old man had undergone six operations within one year on both lacrimal drainage systems. Information about the operations were incomplete, but it was reported that the Jones tubes had been placed bilaterally with subsequent loss of the tubes. The patient was referred for examination and treatment of persistent epiphora. The patient's chief concern was a palpable mass in each lower eyelid.

Bilateral common canalicular obstruction was demonstrated by irrigation and probing. A Jones tube was not visible externally in either medial canthus. Nasal endoscopy identified a Jones tube embedded in each side of the nasal septum with mucopurulent drainage from the lateral walls of the nose (Fig. 3). The lacrimal systems were surgically explored through dacryocystorhinostomy incisions. Each migrated Jones tube was identified and removed from a surrounding inflammatory mass. A residual lacrimal sac was present on each side despite the multiple previous operations, and a bilateral dacryocystorhinostomy was performed. After excision of fibrous tissue around each common internal punctum, it was possible to stent the reconstructed lacrimal drainage pathways with silicone tubing. The tubing has been left in place during the follow-up period of 18 months; the patient has symptomatic tearing only when exposed to cold or wind.

Discussion

Reported complications associated with Jones tubes include obstruction, extrusion, infection, obstruction of the collar of the tube by the surrounding conjunctiva, poor drainage, migration, persistent dacryocystitis, reflux of nasal secretions onto the eye, systemic toxicity from topical eyedrops, hypertrophy of the middle turbinate, damage to the residual canaliculi, diplopia, and tube breakage.[3-12] The incidence of complications is variable; only five of 35

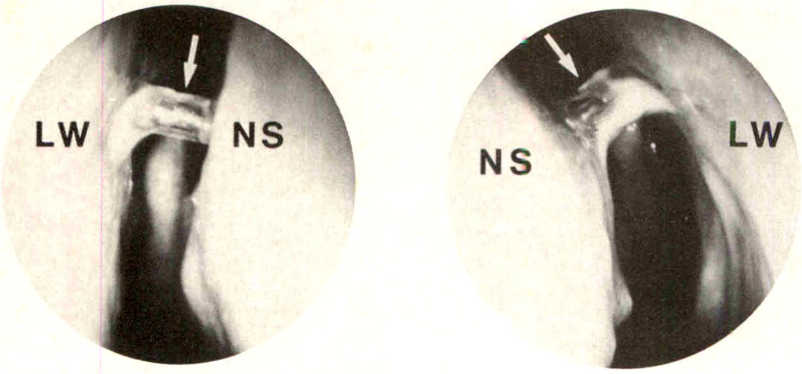


Fig. 3 (Bartley and Gustafson). Case 3. Deeply submerged Jones tubes (arrows) with impaction into nasal septum (NS). LW indicates lateral wall of nose; middle turbinate is visible behind each tube.

patients in the series of Lamping and Levine[7] had problems related to the Jones tube, whereas the complication rate was 50% in the reports by Welham,[5] Medgyesi,[9] and Hurwitz and Howcroft.[6] The functional results of the bypass procedure, however, were excellent (95% in Welham's series and 80% in the patients described by Hurwitz and Howcroft).

In our study, the patient described in Case 1 was treated for episcleritis that initially was not attributed to malposition of the Jones tube. The subsequent development of ipsilateral facial pain and numbness led to a neurologic evaluation before it was recognized that the Jones tube was the source of the problem. In the management of this case, the nasal examination helped establish the diagnosis when the Jones tube was found to be improperly positioned against the nasal septum, and intraoperative nasal endoscopy was invaluable in replacing the Jones tube with the correct size.

Case 2 illustrated that faulty placement and management of Jones tubes may be potentially sight-threatening. The conjunctiva was "sutured tightly" around the prosthesis in the inferior fornix, allowing the collar of each tube to erode the globe. Pressure necrosis of the sclera may have been exacerbated by the administration of ointment and eyedrops containing corticosteroids. An additional complicating feature of this case was the upward orientation of the tubes. The original position is not known, but tears cannot be expected to drain through a tube angled superiorly. Nik, Hurwitz, and Sang[13] demonstrated that the tubes should be placed as vertically as possible from the medial canthus downward into the nose because gravity is the primary determinant of tear flow.

Case 3 demonstrated extreme subconjunctival migration of bilateral Jones tubes, resulting in symmetric inflammatory lower eyelid masses that were the patient's chief concern. Intraoperative exploration of the lacrimal drainage system allowed the residual canaliculi to be salvaged and eliminated the need for the Jones tubes. As in Case 1, preoperative nasal endoscopy was invaluable.

These three cases illustrate that proper placement of the Jones tube and prevention of migration are necessary for its proper function. Migration and extrusion of the Jones tube may be reduced by using a trephine to insert the tube,[14] by placement of a temporary suture around the tube in the immediate postoperative period,[15] by use of a modified Pyrex tube with a second flange that reduces mobility of the tube,[4] or by placing a silicone sleeve around a standard tube to enhance fibrous tissue ingrowth.[16] Regardless of the technique used, both surgeon and patient must recognize that placement of a Jones tube requires long-term maintenance and follow-up by the physician and patient.

References

1. Jones, L. T.: An anatomical approach to problems of the eyelids and lacrimal apparatus. Arch. Ophthalmol. 66:137, 1961.

2. ———: The cure of epiphora due to canalicular disorders, trauma and surgical failures on the lacrimal passages. Trans. Am. Acad. Ophthalmol. Otolaryngol. 66:506, 1962.

3. ———: Conjunctivodacryocystorhinostomy. Am. J. Ophthalmol. 59:773, 1965.

4. Gladstone, G. J., and Putterman, A. M.: A modified glass tube for conjunctivodacryocystorhinostomy. Arch. Ophthalmol. 103:1229, 1985.

5. Welham, R. A N.: Canalicular obstructions and the Lester Jones tube. What to do when all else fails. Trans. Ophthalmol. Soc. U.K. 93:623, 1973.

6. Hurwitz, J. J., and Howcroft, M. J.: Use of Lester Jones tubes. A review of 40 cases. Can. J. Ophthalmol. 16:176, 1981.

7. Lamping, K., and Levine, M. R.: Jones' tubes. How good are they? Arch. Ophthalmol. 101:260, 1983.

8. Putterman, A. M., and Epstein, G.: Combined Jones tube-canalicular intubation and conjunctival dacryocystorhinostomy. Am. J. Ophthalmol. 91:513, 1981.

9. Medgyesi, S.: Tear drainage. Scand. J. Plast. Reconstr. Surg. 11:83, 1977.

10. Wood, J. R., Anderson, R. L., and Edwards, J. J.: Phospholine iodide toxicity and Jones' tubes. Ophthalmology 87:346, 1980.

11. Doucet, T. W., and Hurwitz, J. J.: The broken Lester Jones tube. Can. J. Ophthalmol. 17:32, 1982.

12. Skov, C. M B., and Mazow, M. L.: Diplopia following Jones tube placement. Ophthalmic Surg. 15:932, 1984.

13. Nik, N. A., Hurwitz, J. J., and Sang, H. C.: Mechanism of tear flow after dacryocystorhinostomy and Jones' tube surgery. Arch. Ophthalmol. 102:1643, 1984.

14. Henderson, P. N.: A trephining technique for the insertion of Lester Jones tubes. Arch. Ophthalmol. 85:448, 1971.

15. Putterman, A. M.: Fixation of Pyrex tubes in conjunctivodacryocystorhinostomy. Am. J. Ophthalmol. 78:1026, 1974.

16. Corin, S. M., Hurwitz, J. J., and Tucker, S. M.: A simple technique for the prevention and management of Jones bypass tube extrusion. Can. J. Ophthalmol. 23:322, 1988.

OPHTHALMIC MINIATURE

In a minute the wreath will start to color and I will begin seeing things. That's how tired I am: as when you'd driven all night, into the dawn, for some reason, I won't think about that now, keeping each other awake with stories and taking turns at the wheel, and as the sun would begin to come up you'd see things at the sides of your eyes: purple animals, in the bushes beside the road, the vague outlines of men, which would disappear when you looked at them straight.

Margaret Atwood, *The Handmaid's Tale*
Boston, Houghton Mifflin Company, 1986, p. 128

Class II Antigen Expression in Diabetic Preretinal Membranes

Christophe Baudouin, M.D., William C. Gordon, Ph.D.,
Daniele Fredj-Reygrobellet, Ph.D., Françoise Baudouin, M.D.,
Gholam Peyman, M.D., Pierre Gastaud, M.D.,
and Nicolas G. Bazan, M.D.

Using immunofluorescence and immunoperoxidase procedures, we found large amounts of IgG, IgA, IgM, and IgE, as well as C1q, C3c, and C3d, in the connective stroma and within the vascular walls on eight specimens of preretinal membranes obtained from diabetic patients with proliferative retinopathy. The membranes contained many isolated human leukocyte antigen (HLA) DR- and DQ-expressing cells, and vascular endothelial cells strongly expressed class II determinants. Monoclonal antibodies to immunocompetent cells disclosed only rare B lymphocytes or suppressor/cytotoxic T cells and few monocytes. These findings confirm previous evidence of immune reactions in the pars plana of patients with proliferative diabetic retinopathy, and suggest that an autoimmune reaction is a factor in this complication. It is yet not possible to determine whether this reaction is a nonspecific consequence of the vasoproliferative processes or if it plays a direct role in the *development* and *extension* of preretinal membranes.

RETINAL NEOVASCULARIZATION and the subsequent development and contraction of retinal fibrovascular membranes are a major cause of visual loss in patients with diabetes. Ultrastructural studies show that preretinal membranes consist of blood vessels embedded within a dense collagenous meshwork, which also contains monocytes, lymphocytes, fibroblasts, and glial cells.[1-3] Although extensively studied, the pathogenesis of proliferative diabetic retinopathy remains poorly understood, and the mechanisms leading to retinal neovascularization have not been determined.

Biopsies of pars plana in proliferative diabetic retinopathy by Baudouin and associates[4] demonstrated immunoglobulin and complement deposits, as well as class II major histocompatibility complex antigens at the level of the pigmented epithelium. Because these results suggested that autoimmune phenomena occur in proliferative diabetic retinopathy, we undertook an immunohistologic study of diabetic preretinal membranes to detect similar changes in the new blood vessels, and to test our hypothesis that the immune system is involved in the development of retinal neovascularization.

Material and Methods

Preretinal membranes were excised surgically from eight patients with diabetic proliferative retinopathy undergoing vitrectomy for traction macular detachment (five patients) or nonclearing vitreous hemorrhage (three patients). All of these patients (four men and four women) had insulin-dependent diabetes. The patients' ages ranged from 22 to 42 years.

Specimens were fixed in 2% paraformaldehyde, rinsed in phosphate-buffered saline at pH 7.4, and placed in embedding compound. The specimens were frozen in liquid nitrogen and stored at −80 C before sectioning.

Twenty-two different monoclonal or poly-

Accepted for publication Sept. 13, 1989.

From the Department of Ophthalmology, Saint-Roch Hospital, Nice, France (Drs. C. Baudouin and Gastaud), Departments of Ophthalmology and Pharmacology, School of Medicine, University of Nice (Drs. Fredj-Reygrobellet and F. Baudouin), Department of Ophthalmology, Louisiana State University Eye Center, Louisiana State University Medical Center School of Medicine, New Orleans (Drs. Gordon, Peyman, and Bazan), and Eye, Ear, Nose and Throat Hospital, New Orleans, Louisiana (Dr. Bazan). This study was supported in part by U.S. Public Health Service Grant EY02377 from the National Eye Institute.

Reprint requests to Nicolas G. Bazan, M.D., LSU Eye Center, 2020 Gravier St., Suite B, New Orleans, LA 70112.

clonal antibodies were used in this study. Fluorescein isothiocyanate-conjugated rabbit anti-human IgG, IgM, IgA, IgD, and IgE antisera, as well as four antisera directed against different complement components (C1q, C3c, C3d, and C4), were purchased from Dakopatts, Copenhagen. IgG was also detected with mouse anti-human Fc IgG monoclonal antibody (Immunotech, Marseille). Fluorescein isothiocyanate-labeled anti-factor VIII antiserum (Dakopatts) was used to identify endothelial cells in blood vessels, and anti-insulin antiserum (Dakopatts) was used to detect deposits of exogenous insulin. Three monoclonal antibodies raised against the nonpolymorphic region of the human leukocyte DR antigen (HLA) anti-human DRl (Bethesda Research Laboratories, Gaithersburg, Maryland), I2 (Coulter, Hialeah, Florida), and G157 anti-HLA DR (Dr. Bernard, Gustave Roussy Institute, Paris) were used. We also tested one monoclonal antibody directed against a monomorphic determinant of class II HLA-DQ molecules (IOT2d, Immunotech). Additional monoclonal antibodies were utilized to identify T lymphocytes. OKT11 (Ortho Diagnostic Systems, Raritan, New Jersey) reacted with all peripheral T lymphocytes, and T4 (Becton Dickinson Immunochemistry Systems, Mountain View, California) and OKT8 (Ortho) were directed against helper T lymphocytes and suppressor/cytotoxic T cells, respectively. B lymphocytes were sought using B1 monoclonal antibody (Coulter), natural killer lymphocytes with Leu7 monoclonal antibody (Becton Dickinson), and monocytes using OKM1 monoclonal antibody (Ortho). All monoclonal antibodies were detected with a fluorescein isothiocyanate-labeled rabbit anti-mouse immunoglobulin antiserum (Dakopatts). These reagents were used in a 1:50 dilution in phosphate-buffered saline, except anti-IgG and C3d, which were used in a 1:100 dilution.

Frozen sections (4 μm) were prepared, placed on gelatin-coated slides, and air-dried at room temperature. Sections were washed in phosphate-buffered saline and reacted with each specific antibody according to direct or indirect immunofluorescence procedures. Antisera to immunoglobulins, complement, and factor VIII were incubated for 30 minutes. The other tested antibodies were applied for 90 minutes and then made visible by fluorescein isothiocyanate-conjugated anti-mouse immunoglobulin antiserum. Some of the sections were counterstained with propidium iodide.[5] After the last incubation, sections were washed in phosphate-buffered saline and mounted in mounting medium (AF1 medium, Citifluor Ltd, London).

An immunoperoxidase procedure, using the avidin-biotin peroxidase–complex method, was performed in a previously described manner.[4] After fixation in acetone for ten minutes, sections were incubated for one hour with primary antibodies. After washing in tris(hydroxymethyl)aminomethane-buffered saline, biotin-conjugated horse anti-mouse IgG antiserum was applied for 30 minutes. Avidin-biotin peroxidase complexes (Dakopatts) were then layered for 30 minutes in a 1:100 dilution. The slides were developed in aminoethyl carbazole hydrogen peroxide solution, counterstained with Harris hematoxylin, dehydrated, and placed in mounting medium before examination.

Negative control sections were prepared in each immunostaining procedure by omission of the primary antibodies, or substitution by non-immmune rabbit or mouse serum, to detect any nonspecific binding of the reagents. Hematoxylin-eosin staining was used to histologically visualize sections of each specimen.

Results

Examination of the eight preretinal membranes stained with hematoxylin and eosin showed dense connective tissue surrounding numerous blood vessels (Figure, top left), and isolated, elongated cells presumed to be fibroblasts or glial cells. A few lymphocytes and some neutrophils were also seen.

The staining patterns of the eight specimens are summarized in the Table. Immunoperoxidase analysis disclosed findings similar to those obtained with the immunofluorescence procedure.

A diffuse homogeneous fluorescence for IgG, IgA, and IgE was seen in the connective stroma (Figure, middle left), and the vascular walls were underlined with abundant continuous deposits. Similar deposits of IgM demonstrated a linear pattern (Figure, top right) in the vascular walls at the endothelial level, whereas anti-IgD antiserum did not react. Large complement deposits were also seen in those specimens. With the exception of C4, which was consistently positive (two cases), anti-C1q, C3c, and C3d antisera showed a strong linear fluorescence in the vascular walls, with a reactivity

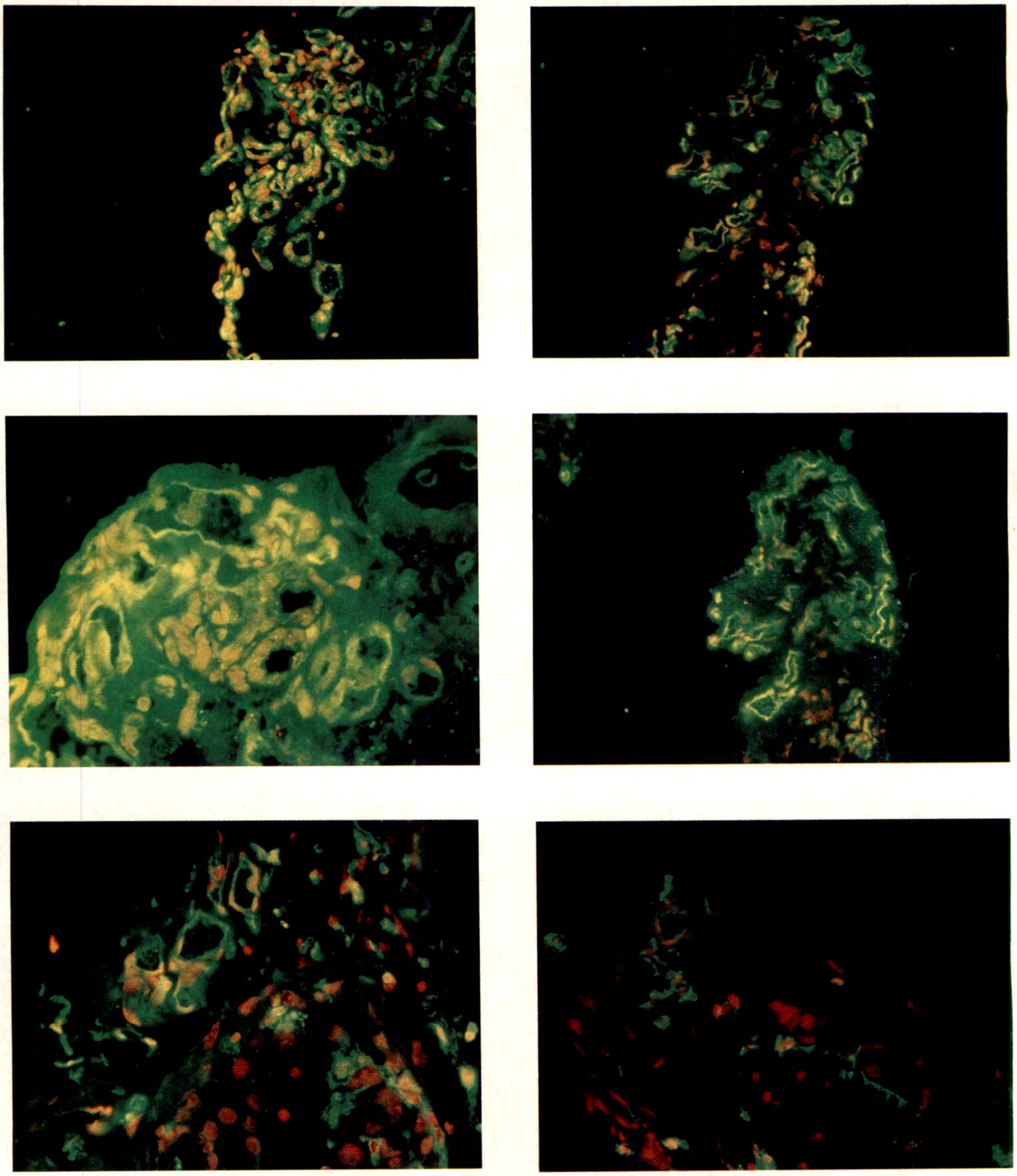


Figure (Baudouin and associates). Top left, Immunofluorescent staining of vascular endothelial cells in a diabetic preretinal membrane reacted with anti-factor VIII antiserum (× 350). Top right, Section of the same membrane incubated with anti-IgM antiserum showing linear deposits of IgM in the capillary walls (× 250). Middle left, Immunofluorescent reactivity of a diabetic preretinal membrane with anti-IgG antiserum. An intense, diffuse staining can be observed in the connective stroma with bright fluorescence concentrated in the vascular walls (× 400). Middle right, Anti-C3c antiserum shows bright vascular reactivity with weak, diffuse staining surrounding blood vessels (× 250). Bottom left, Diabetic preretinal membrane incubated with anti-HLA-DR monoclonal antibody showing bright staining in the vascular walls at the endothelial level, as well as numerous class II-expressing cells scattered throughout the connective stroma (× 400). Bottom right, Membrane fluorescence of HLA-DQ antigens at the surface of spindle-shaped cells isolated in the stroma (× 400).

TABLE
IMMUNOSTAINING REACTIVITY OF PRERETINAL MEMBRANES FROM EIGHT INSULIN-DEPENDENT DIABETIC PATIENTS WITH PROLIFERATIVE RETINOPATHY*

ANTIGENS	ENDOTHELIAL CELLS	VASCULAR WALLS	STROMAL CELLS	CONNECTIVE TISSUE
IgG	+	+	+	+
IgA	+	+	+	+
IgM	+	+	±	−
IgD	−	−	−	−
IgE	+	+	±	±
C1q	+	+	−	+
C3c	+	+	−	−
C3d	+	+	−	−
C4	±	±	−	−
Factor VIII	+	−	−	−
Insulin	−	−	−	−
HLA DR	+	−	+	−
HLA DQ	+	−	+	−
T lymphocytes	−	−	−	−
T helper cells	−	−	−	−
Suppressor/ cytotoxic T cells	−	−	±	−
B lymphocytes	−	−	±	−
Natural killer lymphocytes	−	−	−	−
Monocytes	−	−	±	−

*+ indicates strongly reactive; ±, weakly or inconsistently reactive; −, no reaction.

similar to that seen with anti-immunoglobulin antibodies (Figure, middle right).

Investigations of class II antigens with anti-HLA-DR and -DQ monoclonal antibodies produced the same results. Preretinal membranes contained numerous, scattered class II-expressing cells on which a strong membrane fluorescence could be seen (Figure, bottom left and right). Moreover, vascular endothelial cells (identified by anti-factor VIII reactivity) were brightly positive, both for anti-HLA-DR and -DQ monoclonal antibodies (Figure, bottom left). A minority of the isolated stromal cells appeared to be monocytes (OKM1-positive), suppressor/cytotoxic T lymphocytes (OKT8-positive), or B lymphocytes (B1-positive), but the three other monoclonal antibodies used to identify immunocompetent cells (T3, T4, and Leu 7) produced negative results.

Discussion

Some reports have implicated the immune system in diabetic retinopathy.[6,7] Baudouin and associates[4] reported immunoglobulin and complement deposition at the basal pole of pigmented epithelial cells of the pars plana as well as an abnormal expression of HLA-DR antigens by pigmented and nonpigmented epithelial cells. In this study, we confirmed the occurrence of immune phenomena in proliferative diabetic retinopathy because preretinal membranes contain massive deposits of immunoglobulins and activated complement components. It is noteworthy that four different classes of immunoglobulins, including IgE, as well as the complement components, accumulate in the vascular walls in a linear pattern. These results are consistent with those of Melato and associates[7] who found IgG, IgA, and IgM deposits in the walls of newly formed preretinal vessels. This study describes three major markers of immune phenomena (immunoglobulins, complement system, and, especially, class II antigen expression) by growing cells.

HLA-DR and -DQ antigens are normally restricted to immunocompetent cells and play an important regulatory role in the immune response. Their aberrant expression has been found on nonlymphoid cells in various autoimmune diseases.[8,9] Bottazzo and associates[10] suggested that abnormal expression by the target cells could be the initial event in autoimmune phenomena, converting those cells into functional antigen-presenting cells, allowing helper T lymphocyte activation and subsequent autoimmune reaction.

In our study, endothelial cells strongly expressed class II determinants. These cells were also surrounded by large amounts of immunoglobulin and complement deposits, suggesting immune phenomena at their level, either by fixation of circulating immune complexes or by direct autoantibody production. The absence of reactivity of anti-insulin antiserum seems to eliminate the previously suggested role of insulin-containing immune complexes.[6] These endothelial cells, however, were not the only HLA-DR and -DQ expressing cells, because numerous other nonvascular cells, scattered throughout the connective stroma, were also found. The origin of these cells could not be determined, although some were identified as

monocytes (OKM1-positive), suppressor/cytotoxic T lymphocytes (OKT8-positive), or B lymphocytes (B1-positive). Mechanisms of this strong expression of class II antigens by cellular components of preretinal membranes remain unknown. However, as shown previously,[11] neither ocular fibroblast-related cells nor retinal vascular endothelial cells normally express HLA-DR and -DQ determinants or contain immunoglobulin or complement deposits. Our data demonstrate major functional changes induced in target cells by proliferative phenomena. It may be hypothesized that this immune reaction results from direct stimulation by growth-promoting factors. Peptide growth factors such as platelet-derived growth factor, epidermal growth factor, and fibroblast growth factor have been found[12] to stimulate the production of interferon gamma, a potent inducer of HLA-DR expression in many different cells, both in vivo and in vitro.[13-15] It could be suggested that the liberation of various growth factors by the damaged retina may stimulate interferon gamma production, and thus HLA-DR or -DQ expression by the growing cells, resulting in the development of an immune response, with secondary immunoglobulin deposits and complement activation.

Whether such an immune reaction, located at the proliferating cell level, is a nonspecific consequence of vasoproliferative processes, or plays a direct role in the extension of fibrovascular tissue, remains to be determined. Numerous questions remain unanswered, but a better knowledge of the involvement of the immune system in proliferative diabetic retinopathy will be of great importance in the understanding of the pathogenesis of this disease.

References

1. Hamilton, C. W., Chandler, D., Klintworth, G. K., and Machemer, R.: A transmission and scanning electron microscopic study of surgically excised preretinal membrane proliferations in diabetes mellitus. Am. J. Ophthalmol. 94:473, 1982.
2. Jerdan, J. A., Michels, R. G., and Glaser, B. M.: Diabetic preretinal membranes. An immunohistochemical study. Arch. Ophthalmol. 104:286, 1986.
3. Williams, J. M., de Juan, E., Jr., and Machemer, R.: Ultrastructural characteristics of new vessels in proliferative diabetic retinopathy. Am. J. Ophthalmol. 105:491, 1988.
4. Baudouin, C., Fredj-Reygrobellet, D., Lapalus, P., and Gastaud, P.: Immunohistopathologic findings in proliferative diabetic retinopathy. Am. J. Ophthalmol. 105:383, 1988.
5. Yeh, C. J G., Hsi, B. L., and Faulk, W. P.: Propidium iodide as a nuclear marker in immunofluorescence. II. Use with cellular identification and viability studies. J. Immunol. Methods 43:269, 1981.
6. Shabo, A. L., and Maxwell, D. S.: Insulin-induced immunogenic retinopathy resembling the retinitis proliferans of diabetes. Trans. Am. Acad. Ophthalmol. Otolaryngol. 81:497, 1975.
7. Melato, M., Antonutto, G., Manconi, R., and Ponte, E.: Ocular deposits of immunoglobulin in diabetic retinopathy. Can. J. Ophthalmol. 17:45, 1982.
8. Hanafusa, T., Pujol-Borrell, R., Chiovato, L., Russell, R. C G., Doniach, D., and Bottazzo, G. F.: Aberrant expression of HLA DR antigen on thyrocytes of Graves' disease. Relevance for autoimmunity. Lancet 2:1111, 1983.
9. Foulis, A. K., and Farquharson, M. A.: Aberrant expression of HLA DR antigens by insulin-containing cells in recent-onset type I diabetes mellitus. Diabetes 35:1215, 1986.
10. Bottazzo, G. F., Pujol-Borrel, R., Hanafusa, T., and Feldmann, M.: Role of aberrant HLA DR expression and antigen presentation in induction of endocrine auto-immunity. Lancet 2:1115, 1983.
11. Baudouin, C., Fredj-Reygrobellet, D., Gastaud, P., and Lapalus, P.: HLA DR and DQ distribution in normal human ocular structures. Curr. Eye Res. 7:903, 1988.
12. Johnson, H. M., and Torres, B. A.: Peptide growth factors PDGF, EGF, and FGF regulate interferon gamma production. J. Immunol. 134:2824, 1985.
13. Geppert, T. D., and Lipsky, P. E.: Antigen presentation by interferon gamma-treated endothelial cells and fibroblasts. Differential ability to function as antigen-presenting cells despite comparable Ia expression. J. Immunol. 135:3750, 1985.
14. Todd, I., Pujol-Borrel, R., Hammond, L. J., Bottazzo, G. F., and Feldmann, M.: Interferon gamma induces HLA DR expression by thyroid epithelium. Clin. Exp. Immunol. 61:265, 1985.
15. Detrick, B., Newsome, D. A., Percopo, C. M., and Hooks, J. J.: Class II antigen expression and gamma interferon modulation of monocytes and retinal pigment epithelial cells from patients with retinitis pigmentosa. Clin. Immunol. Immunopathol. 36:201, 1985.

Auditory Function in Duane's Retraction Syndrome

A. Ro, M.D., G. Chernoff, M.D., D. MacRae, M.D.,
R. B. Orton, M.D., and W. Cadera, M.D.

We obtained audiograms and auditory brainstem responses from 44 patients with Duane's retraction syndrome to assess the incidence and nature of hearing deficit. Of 44 patients, seven (15.9%) had evidence of hearing impairment. Three (6.8%) subjects had a temporary conductive hearing loss because of middle ear fluid, and another patient had hearing loss from Crouzon's disease. The remaining three (6.8%) patients demonstrated sensorineural hearing deficit. This hearing impairment was attributed to a cochlear lesion and not to a pontine lesion. We believe that the frequency of sensorineural hearing loss in these patients warrants hearing screening programs similar to those used for infants in neonatal intensive care units.

DUANE'S RETRACTION SYNDROME is a congenital ocular motility disorder that is present in approximately 1% of those with strabismus.[1,2] It is characterized by complete or partial deficiency of abduction; complete or partial deficiency of adduction; narrowing of palpebral fissure with adduction; retraction of globe with adduction; oblique up or down movement with adduction; and deficiency of convergence.

Since the first report by Alexander Duane in 1905,[3] many studies have described abnormalities associated with Duane's syndrome. In 1980, Jay and Hoyt[4] implicated pontine anomalies as a possible cause of Duane's syndrome, because in nine of 14 Duane's retraction syndrome patients, abnormal auditory brainstem responses were noted. Subsequent studies by Taylor and Polomeno,[5] and Parkinson and Tompkin[6] have not supported their findings.

We measured auditory brainstem responses and evaluated audiograms from 44 patients with Duane's syndrome to understand audiometric findings in these patients better and to determine objectively the incidence of hearing deficit in Duane's retraction syndrome.

Subjects and Methods

Twenty females and 24 males with Duane's retraction syndrome diagnosed at our institution were studied. The patients' ages ranged from 1 to 50 years. Nineteen patients had the left eye involved, nine had the right eye involved, and the remaining 16 patients had involvement of both eyes. None of the patients had Goldenhaar's syndrome or Klippel-Feil syndrome. One patient, however, had Crouzon's disease. All patients were classified according to Huber's system.[7]

All 44 patients underwent audiologic examination, which included, in 41 patients, pure-tone audiogram, speech audiometry, tympanometry, and acoustic reflexes. Three children, who were unable to respond to single ear audiometric testing, underwent behavior observation audiometry. Auditory brainstem responses were recorded in all 44 patients by using the Nicolet CA-1000 evoked response system with low and high pass filter settings of 150 Hz and 3 kHz, respectively. The subjects were seated, and electrodes were placed on the midforehead and on each mastoid process. The electrode impedance was less than 5 kilohms and was bilaterally consistent in all subjects. Clicks were presented to each ear at a rate of 33.3/sec with a duration of 100 msec. An average of 2,000 clicks was presented at each intensity level. Clicks were presented at intensities of 75 and 95 dB using masking levels of 50 dB in the nontested ear to avoid cross-stimulation. The behavior of waves I, III, and V from the

Accepted for publication Oct. 9, 1989.
From the Ivey Institute of Ophthalmology, Departments of Ophthalmology (Drs. Ro, Orton, and Cadera) and Otolaryngology (Drs. Chernoff and MacRae), University of Western Ontario, Ontario, Canada.
Reprint requests to W. Cadera, M.D., Ivey Institute of Ophthalmology, P.O. Box 5375, Station A, London, Ontario, Canada, N6A 4G5.

auditory pathway was then evaluated in each patient.

Results

Thirty-seven patients had normal hearing as determined by audiometry and auditory brainstem response. On auditory brainstem response, latencies of waves I, III, and V were within two standard deviations of normal and were, therefore, considered to be normal. The remaining seven patients were found to a have a hearing deficit. Three of these patients demonstrated mild-to-moderate conductive hearing loss. The audiograms showed tympanograms indicative of middle ear effusion. Auditory brainstem response displayed waveform delay consistent with conductive hearing loss. One patient had a partial bilateral hearing loss attributable to Crouzon's disease.

The remaining three patients had neurosensory hearing loss. The first patient was an 11-year-old girl with left type I Duane's syndrome. She had no other ocular or systemic problems. Audiometry disclosed a profound left neurosensory hearing loss starting at the 2,000-Hz level. Speech reception threshold for the left ear was 10 dB with 94% word discrimination as compared to 0 dB with 98% discrimination on the right side. On auditory brainstem response, left ear latencies were 3.82 msec for wave III and 5.80 msec for wave V, as compared to 3.66 msec and 5.62 msec for waves III and V on the right side, respectively.

The second patient with neurosensory hearing deficit was a 10-year-old boy. He had bilateral type I Duane's syndrome (greater in the right eye than the left) with a profound right hearing loss. Speech reception threshold for the left ear was 10 dB with 100% discrimination. Speech reception threshold for the right ear was 103+ dB. Word discrimination could not be tested in this ear. Auditory brainstem response showed normal wave forms in the left ear with wave III and wave V latencies of 3.68 msec and 5.58 msec, respectively. In the right ear, however, there was no brainstem response, including wave I.

The third patient affected was a 40-year-old woman with a bilateral (left type III greater than right type I) Duane's syndrome. She had no other ocular or systemic problems, and there was no family history of hearing impairment. On audiometry, she had a moderately severe left neurosensory hearing loss above 1,000 Hz and a profound right hearing loss. Tympanograms were normal bilaterally. Speech reception threshold was 10 dB hearing level on the left with 100% word discrimination. On the right ear, it was 100+ dB with no detectable discrimination. On auditory brainstem response, waves were normal in the left ear with wave III and wave V latencies of 3.64 msec and 5.72 msec, respectively. In the right ear, no consistent waves were detectable.

Discussion

In assessing those with Duane's retraction syndrome using auditory brainstem response, one has to first consider the structures in the auditory pathway in the brain stem and the different waves generated by these structures. Auditory brainstem responses are measures of electrical activity from the structures in the auditory pathway. They have been used extensively to locate brainstem lesions, such as neoplasms and demyelinating diseases.

A series of seven waves is produced. It has been shown that waves I to VII come from the acoustic nerve, cochlear nuclei, superior olives, lateral lemnisci, inferior colliculi, medial geniculate, and auditory radiation, respectively[8-10] (Figure).

Using auditory brainstem response, Jay and Hoyt[4] found that nine of 14 Duane's syndrome patients they studied had increased latency of wave III, suggesting a pontine lesion. However, two subsequent studies, in which 16 and 15 patients were studied, have failed to support this.[5,6]

Of the 44 Duane's syndrome patients we studied, none had increased latency of waves III or V, supporting the findings of Taylor and Polomeno,[5] and Parkinson and Tompkins,[6] who also failed to show increased latencies of waves III and V in 16 and 15 patients with Duane's syndrome, respectively. In one patient with bilateral sensorineural hearing loss, we were unable to show isolated increased latency of wave III and V in one ear. In the other ear, we could not detect any wave forms, including wave I, which indicated a lesion at the cochlear level. In the two patients with unilateral sensorineural hearing abnormality, latencies of wave III and V in the affected ear in one patient were normal, and in the other patient no brainstem response was observed in the affected ear,

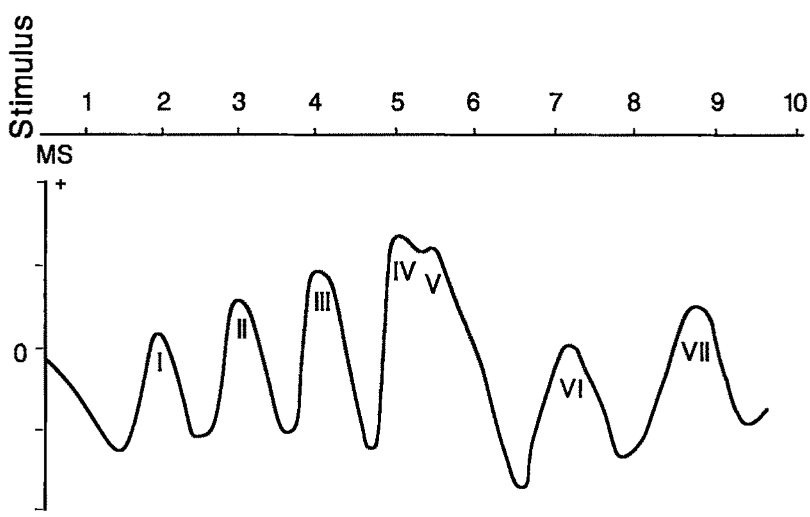


Figure (Ro and associates). Components of auditory-evoked response. I, auditory nerve; II, cochlear nuclei; III, superior olivary complex; IV, lateral lemniscus; V, inferior colliculus; VI, medial geniculate; and VII, auditory radiations.

which again suggested the existence of a cochlear lesion. In three patients with sensorineural hearing deficits, the only consistent abnormalities in auditory brainstem response were unrecognizable wave forms, indicating that the lesion site was located in the cochlear area in the auditory pathway.

In studies of Duane's retraction syndrome, the incidence of sensorineural hearing loss has been said to range from 1% to 11%.[11] In 1970, Kirkham[1] reported that 12 of 112 (10.7%) of his patients with Duane's syndrome had perceptive deafness. Pfaffenbach, Cross, and Kearns[12] stated that 6.4% had sensorineural deafness in their series of 186 Duane's patients. On the other hand, O'Malley, Helveston, and Ellis[13] described only one of 97 (1%) with sporadic bilateral nerve deafness. In all these studies, however, the basis on which sensorineural deafness was diagnosed in their respective Duane's retraction syndrome patients was not described. Additionally, anatomic lesions corresponding to sensorineural hearing loss were not discussed. The subsequent studies using auditory brainstem response to better quantify the hearing loss in Duane's patients[4-6] have produced conflicting results in small numbers of subjects.

In our series of patients, seven of 44 patients (15.9%) demonstrated objective evidence of hearing deficit. Excluding conductive and structural causes, three of 44 patients (6.8%) had sensorineural hearing impairment. Auditory brainstem response indicated that the likely lesion was in the cochlear region.

The incidence of hearing impairment in the newborn population has been reported to be approximately 0.1%.[14,15] When our results are compared with this finding, the rate of sensorineural hearing deficit in the Duane's group is significantly high. The rate is, however, comparable to the reported incidence of hearing impairment in infants at high risk and infants from neonatal intensive care units.[15,16] Because of this high incidence, otolaryngologists and audiologists have advocated screening these infants with auditory brainstem response measurements so that necessary medical intervention and educational support can be implemented early. Based on our data, we believe that similar screening programs in those with Duane's syndrome should be considered.

References

1. Kirkham, T. H.: Inheritance of Duane's syndrome. Br. J. Ophthalmol. 54:323, 1970.

2. White, J. W., and Brown, H. W.: Occurrence of vertical anomalies associated with convergent and divergent anomalies. Arch. Ophthalmol. 21:999, 1939.

3. Duane, A.: Congenital deficiency of abduction, associated with impairment of adduction, retraction movements, contraction of the palpebral fissure and oblique movements of the eye. Arch. Ophthalmol. 34:133, 1905.

4. Jay, W. M., and Hoyt, C. S.: Abnormal brain stem auditory-evoked potentials in Stilling-Türk-Duane retraction syndrome. Am. J. Ophthalmol. 89:814, 1980.

5. Taylor, M. J., and Polomeno, R. C.: Further observations on the auditory brainstem response in Duane's syndrome. Can. J. Ophthalmol. 18:238, 1983.
6. Parkinson, J., and Tompkins, C.: Auditory brainstem response in Duane's retraction syndrome. Am. Orthoptic J. 32:121, 1982.
7. Huber, A.: Electrophysiology of the retraction syndromes. Br. J. Ophthalmol. 58:293, 1974.
8. Starr, A., and Achor, L. J.: Auditory brainstem responses in neurologic diseases. Arch. Neurol. 32:761, 1975.
9. Stockard, J. J., and Rossiter, V. S.: Clinical and pathologic correlates of brain stem auditory response abnormalities. Neurology 27:316, 1977.
10. Picton, T. W., and Durieux-Smith, A. D.: The practice of evoked potential audiometry. Otolaryngol. Clin. North Am. 11:263, 1978.
11. Ro, A., Gummeson, B., Orton, R. B., and Cadera, W.: Duane's retraction syndrome. Southwestern Ontario experience. Can. J. Ophthalmol. 24:200, 1989.
12. Pfaffenbach, D. D., Cross, H. E., and Kearns, T. P.: Congenital anomalies in Duane's retraction syndrome. Arch. Ophthalmol. 88:635, 1972.
13. O'Malley, E. R., Helveston, E. M., and Ellis, F. D.: Duane's retraction syndrome—plus. J. Pediatr. Ophthalmol. Strabismus 19:161, 1982.
14. Fria, T. J.: Assessment of hearing. Pediatr. Clin. North Am. 28:757, 1981.
15. Sanders, R., Durieux-Smith, A., Hyde, M., Jacobson, J., Kileny, P., and Murnane, O.: Incidence of hearing loss in high risk and intensive care nursery infants. J. Otolaryngol. 14(suppl.):28, 1985.
16. Schulman-Galambos, C., and Galambos, R.: Brain stem evoked response audiometry in newborn hearing screening. Arch. Otolaryngol. 105:86, 1979.

OPHTHALMIC MINIATURE

To remove a Scum or Skin from the Eye—Before sunrise on St. Bartholomew's day, you must dig up four or five roots of the dandelion weed, taking good care to get the ends of the roots; then you must procure a rag and a thread that have never been in the water; the thread, which dare not have a single knot in it, is used in sewing up the roots into the rag, and the whole is then to be hanged before the eye until the scum disappears. The tape by which it is fastened, must never have been in the water.

John George Hohman, *The Long Lost Friend*
Near Reading, Harrisburg, Pa, 1850, p. 27

The Medial Rectus Muscle Insertion Site in Infantile Esotropia

Ronald V. Keech, M.D., William E. Scott, M.D., and John D. Baker, M.D.

The distance from the corneoscleral limbus to the insertion site of the medial rectus muscle was measured at several stages of medial rectus recession surgery in 20 patients (40 eyes) with infantile esotropia. Disinsertion of the medial rectus muscle resulted in a mean reduction in the distance from the muscle insertion site to the corneoscleral limbus of 0.903 mm ($P < .001$), whereas the use of fixation forceps on the insertion to abduct the eye resulted in an additional mean reduction of 0.306 mm ($P < .01$). The strabismus surgeon often uses the muscle insertion site as a reference point in determining the desired location for recessing a muscle. Our results suggest that this method of measurement is unreliable in infantile esotropia because the position of the medial rectus muscle insertion site varies considerably during surgery.

THE RECESSION of the medial rectus muscle for infantile esotropia is usually measured from the muscle insertion site.[1-6] In our experience, the distance of the insertion site of the medial rectus muscle from the corneoscleral limbus in infantile esotropia varies during muscle surgery. This variability results in an unstable reference point for measuring a muscle recession. To evaluate the variability of the medial rectus muscle insertion site, we measured, in 40 eyes of 20 patients, the distance between the corneoscleral limbus and the insertion site during different stages of bilateral medial rectus recessions for infantile esotropia.

Accepted for publication Oct. 25, 1989.
From the Department of Ophthalmology, University of Iowa Hospitals and Clinics, Iowa City, Iowa (Drs. Keech and Scott) and Michigan Children's Hospital, Detroit, Michigan (Dr. Baker).
Reprint requests to Ronald V. Keech, M.D., Department of Ophthalmology, University of Iowa Hospitals and Clinics, Iowa City, IA 52242.

Subjects and Methods

Only patients with esotropia documented before six months of age were included in the study. Patients with accommodative esotropia, other ocular abnormalities, or neurologic disorders were excluded.

Bilateral medial rectus recessions were all or part of every patient's operation. Measurements were taken at surgery from the corneoscleral limbus at the 3:00 o'clock meridian in the right eye and at the 9:00 o'clock meridian in the left eye to the insertion site of the medial rectus muscle. The corneoscleral limbus was measured at the anterior junction between the transparent cornea and the gray of the corneoscleral limbus. The muscle insertion site was measured where the most anterior muscle tendon fibers visibly attach to the sclera halfway between the superior and inferior poles of the insertion. We defined the muscle insertion site as the location where the medial rectus muscle tendon is attached to the sclera before disinsertion, and where the medial rectus muscle stump remains after disinsertion of the muscle.

The distance between the corneoscleral limbus and the insertion site of the medial rectus muscle was measured at four different stages of surgery (Figs. 1 to 4): (1) before disinsertion of the muscle with the eye abducted by fixation forceps at the 6:00 and 12:00 o'clock meridian of the corneoscleral limbus; (2) before disinsertion of the muscle with the eye abducted by a muscle hook under the medial rectus muscle; (3) after disinsertion of the muscle with the eye abducted by fixation forceps at the 6:00 and 12:00 o'clock meridian of the corneoscleral limbus; and (4) after disinsertion of the muscle with the eye abducted by fixation forceps at the superior and inferior poles of the muscle insertion site.

All measurements were obtained with the following method: a vernier caliper was modified by placing a groove in each jaw to accept

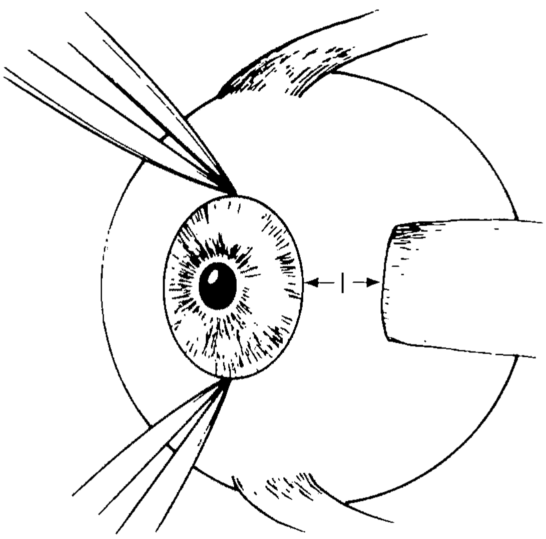


Fig. 1 (Keech, Scott, and Baker). Measurement I. Before disinsertion of the muscle with the eye abducted by fixation forceps and the 6:00 and 12:00 o'clock meridian of the corneoscleral limbus.

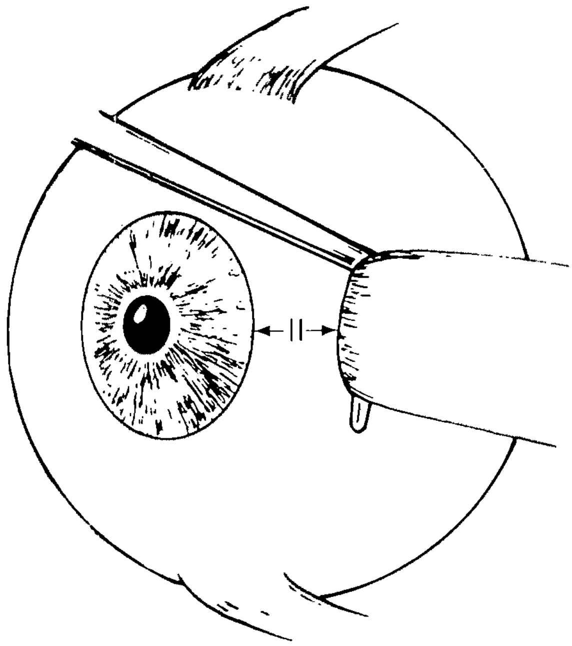


Fig. 2 (Keech, Scott, and Baker). Measurement II. Before disinsertion of the muscle with the eye abducted by a muscle hook under the medial rectus muscle.

the tips of a standard Castroviejo caliper. The distance from the corneoscleral limbus to the muscle insertion was measured with a Castroviejo caliper. The distance between the tips of the Castroviejo caliper was measured with the vernier caliper, and readings were recorded by a technician. All readings were masked to the surgeon.

To assess observer accuracy, all measurements were repeated. Additionally, five patients were measured by two different observers who measured each eye alternately (that is, every measurement on one eye was repeated according to the pattern: observer 1, observer 2, observer 1, and the contralateral eye was measured according to the pattern: observer 2, observer 1, observer 2). These observations were used to determine the accuracy between observers for measurement at each stage of the study.

In six eyes, an additional measurement was made from the medial corneoscleral limbus to a cautery mark placed on the sclera 10 mm from the corneoscleral limbus just superior or inferior to the medial rectus muscle. This mark was placed and measured as soon as possible at the onset of the operation and remeasured just before suturing the recessed medial rectus muscle to the sclera. In 28 eyes, the distance from the corneoscleral limbus to where the recessed muscle was sutured to the sclera was measured just before and after reattachment of the muscle. The scleral cautery mark and the location of the muscle reattachment were measured with the same techniques described for measuring

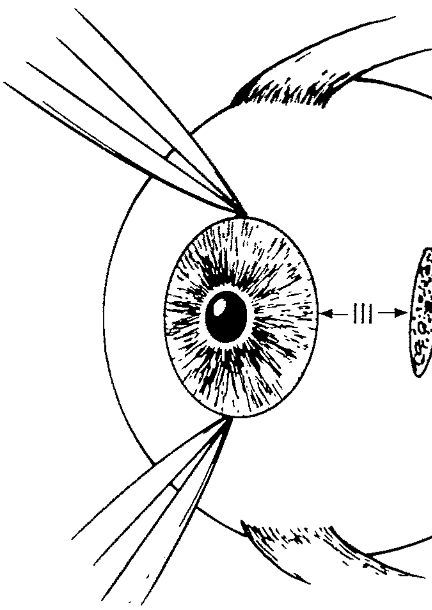


Fig. 3 (Keech, Scott, and Baker). Measurement III. After disinsertion of the muscle with the eye abducted by fixation forceps at the 6:00 and 12:00 o'clock meridian of the corneoscleral limbus.

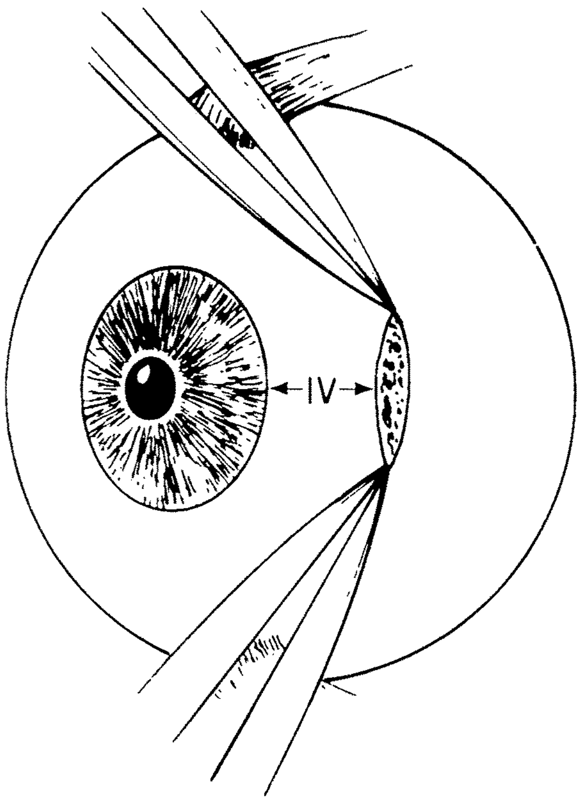


Fig. 4 (Keech, Scott, and Baker). Measurement IV. After disinsertion of the muscle with the eye abducted by fixation forceps at the superior and inferior poles of the muscle insertion site.

the muscle insertion site, except that each measurement was not repeated.

Results

We examined 40 eyes of 20 patients. The mean age at surgery was 16 months (range, 7 to 31 months). Ten patients were 12 months of age or younger at the time of surgery. The mean deviation before surgery was 55 prism diopters of esotropia (range, 35 to 80 prism diopters).

The measurement of the distance of the corneoscleral limbus to muscle insertion was analyzed with analysis of variance and variance components methods. To examine the variability and the relative precision, F-tests for homogeneity of variance were performed. Unless otherwise noted, *t*-tests were used to test for biases and differences between means. In testing differences between the mean measurements at two stages of operation, comparisons were restricted to the subgroup of patients in whom both measurements were taken. In each case, it was verified that the subgroup was representative of the entire sample.

TABLE 1
OBSERVER REPRODUCIBILITY

	EYES (NO.)	VARIANCE	STANDARD DEVIATION (MM)
Intraobserver (all measurements)			
Observer 1	54	0.0123	0.1111
Observer 2	28	0.0234	0.1531
Observer 3	53	0.0119	0.1090
Intraobserver			
Measurement I	20	0.0181	0.1344
Measurement II	39	0.0114	0.1065
Measurement III	39	0.0135	0.1160
Measurement IV	37	0.0169	0.1300
Interobserver			
Measurement I	8	0.0104	0.1021
Measurement II	8	0.0199	0.1411
Measurement III	8	0.0644	0.2538
Measurement IV	8	0.0691	0.2629
Intraobserver (pooled, 135 eye-observer pairs)	—	0.0145	0.1203
Interobserver (pooled, 16 eye-observer pairs)			
Measurements I and II	—	0.0151	0.1232
Measurements III and IV	—	0.0668	0.2359

The precision of the various measurements is noted in Table 1. The intraobserver variance, based on the difference of replicated measurements by each single observer, did not differ significantly among the three observers for any of the four measurements or the overall combined measurements. No observer was consistently more precise than the others ($P > .25$). The differences between replicated measurements ranged from 0.00 to 0.38 mm for observer 1, 0.00 to 0.40 mm for observer 2, and 0.00 to 0.40 mm for observer 3.

The intraobserver variance was also remarkably similar for the four different measurements ($P > .25$). Based on the total data, standard deviations for the measurements ranged from 0.1065 for measurement II to 0.1344 for measurement I; the difference among these was not statistically or clinically significant. The range of differences between repeated measurements by the same observer was also close to identical for the four measurements: 0.00 to 0.40 mm for measurement I, 0.00 to 0.34 mm for measurement II, 0.00 to 0.38 mm for measurement III, and 0.00 to 0.40 mm for measurement IV. Therefore, the overall pooled intraobserver variance was used in testing differences in means.

TABLE 2
MEAN INTRAOPERATIVE MEASUREMENT OF THE DISTANCE BETWEEN THE CORNEOSCLERAL LIMBUS AND THE MEDIAL RECTUS MUSCLE INSERTION SITE

	EYES (NO.)	MEASUREMENTS (MM)			
		I	II	III	IV
Subgroup 1	22	5.302	5.255	—	—
Subgroup 2*	38	—	5.318	4.408	4.102
All patients	40	—	5.312	4.409	—

*One patient did not have measurement IV.

The interobserver variances for measurements I and II were comparable and only slightly greater than the intraobserver variance for the same patients. The observers did not reproduce each other's results as closely for measurements III and IV. Although there was no consistent difference or bias between observers ($P > .25$), their measurements differed by a significantly greater amount ($P < .01$) than for the measurements before muscle disinsertion. A comparison of interobserver measurements III and IV showed no significant difference in precision ($P > .5$). The standard deviation for III and IV, however, was more than twice the standard deviation found for measurements I and II ($P < .01$).

The means of the distance from the corneoscleral limbus to muscle insertion site for the four different measurements are shown in Table 2. The statistical significance of the differences in the means are shown in Table 3. Based on the first 11 patients, measurements I and II did not differ significantly with respect to either the mean ($P > .5$) or variability. Thus, to save time at surgery, measurement I was not made on the last nine patients in the study, and only measurement II was used for comparison with the other measurements. The difference between measurement II and either measurement after disinsertion (III or IV) was highly significant ($P < .001$). A reduction in the corneoscleral limbus to muscle insertion site distance with disinsertion of the muscle occurred in every patient measured. The mean distance for measurement II was 0.903 mm (range, 0.10 to 2.215 mm) greater than the mean for measurement III and 1.22 mm (range, 0.440 to 2.910 mm) greater than the mean for measurement IV. The mean difference in the measurement after muscle disinsertion with fixation at the corneoscleral limbus (measurement III) compared with fixation at the muscle insertion site (measurement IV) was 0.3061 mm ($P < .01$) with a range from −0.255 to 1.245 mm. When the 46 pairs of observer measurements were compared, measurement IV exceeded measurement III in only four cases ($P < .01$, sign test).

TABLE 3
DIFFERENCES IN MEASUREMENTS AND STATISTICAL SIGNIFICANCE*

MEASUREMENTS	DISTANCE (MM)	P VALUE†
I − II	0.046	NS
II − III	0.903	<.001
II − IV	1.22	<.001
III − IV	0.306	<.01

**t*-test, 135 degrees of freedom (df).
†NS indicates not significant.

The means and ranges for measurements I through IV were not significantly different ($P > .025$) when comparing right and left eyes, the patient's sex, or patient's age at surgery.

The distance of the posterior scleral cautery mark from the corneoscleral limbus were measured at the start and completion of surgery in six eyes. The difference in these measurements for each eye ranged from 0.00 to 0.40 mm. A comparison of the initial mean distance of 10.42 mm with the final mean distance of 10.32 mm showed no significant difference ($P > .05$).

The distance from the corneoscleral limbus to where the recessed muscle was sutured to the sclera was measured in 28 eyes before and after reattachment of the muscle. The difference in these measurements for each eye ranged from 0.00 to 0.50 mm. There was no significant difference ($P > .50$) between the mean distance before reattachment of the muscle of 11.08 mm and the mean distance after reattachment of 11.07 mm.

Discussion

Our study documents a statistically and clinically significant anterior displacement of the medial rectus muscle insertion site during surgery for infantile esotropia. The greatest change in the insertion site position (0.903 mm) occurred with disinsertion of the muscle. This change is thought to be caused by the elimina-

tion of the posteriorly directed pull on the insertion by the muscle. A less important but significant factor is the technique used for stabilization of the globe. The application of fixation forceps at the superior and inferior poles of the muscle insertion site was associated with an additional anterior displacement of the insertion of 0.306 mm.

The site of the medial rectus muscle insertion in infantile esotropia is clinically important because strabismus surgeons often rely on it as a point of reference during muscle recession surgery. The traditional surgical procedure is to detach the muscle from the sclera, stabilize the eye with forceps at the superior and inferior poles of the muscle insertion site, and measure the amount of muscle recession from the muscle insertion site. Our study has shown that this technique is unreliable because the site of the muscle insertion is displaced closer to the corneoscleral limbus by an unpredictable amount (0.440 to 2.910 mm) during the course of surgery.

We have found it more accurate in muscle recession surgery to measure from the corneoscleral limbus. For example, if the site of the muscle insertion is 5.5 mm from the corneoscleral limbus before disinsertion of the muscle, and a 5.0-mm muscle recession is desired, then the muscle is recessed and attached to the eye 10.5 mm from the corneoscleral limbus.

Other investigators have also noted a change in the muscle insertion site. Apt and Call[7] suggested that there is a 0.5-mm to 1.0-mm anterior displacement of the insertion site after the disinsertion of the muscle. Kushner, Preslan, and Vrabec[8] found an anterior displacement of the muscle insertion site at surgery in 26 of 80 eyes. They attributed this change to the anterior pull of the fixation forceps, which caused a lamellar tearing of the sclera at the site of the insertion in some patients and a generalized compressibility of the sclera in others.

From a study of 100 consecutive adult autopsy eyes, Apt[9] concluded that there is a factitious displacement of the insertion site when the muscle is removed from the globe. He suggested that this artifact is caused by the surgeon measuring from the corneoscleral limbus to the posterior margin of the insertion site when a muscle hook is placed under the muscle. Our study does not support this conclusion. There was no significant difference ($P > .5$) when the corneoscleral limbus to muscle insertion site distance was measured with or without the muscle hook (measurement I and II).

All measurements in this study were carefully controlled. We developed a modified vernier caliper with an accuracy of 0.05 mm. The measurements of each observer were tested and found to be highly reproducible as were the interobserver measurements for I and II. The interobserver measurements for III and IV, however, were less reproducible, which is documented by the increased standard deviation. The greater variation in measurement III and IV was thought to be caused by the difficulty in distinguishing the junction of the anterior muscle insertion site after disinsertion of the muscle. Only the intraobserver comparisons of measurements, therefore, were used to evaluate the differences in means.

The variability in measurement of a recessed muscle because of anterior displacement of the insertion site will be reduced if the sclera posterior to the muscle insertion is also anteriorly displaced. Of the 26 eyes with anterior displacement of the muscle insertion site noted by Kushner, Preslan, and Vrabec,[8] 22 also had anterior displacement of the posterior sclera. In contrast, we found no significant difference ($P > .05$) in the distance from the corneoscleral limbus to a posterior scleral mark measured at the start and completion of surgery in six eyes. Moreover, the distance from the corneoscleral limbus to where the muscle was sutured to the sclera did not vary significantly when compared before and after reattachment of the muscle. These findings suggest that anterior displacement of the muscle insertion site is not routinely offset by anterior displacement of the posterior sclera.

Our study shows that intraoperative manipulation may result in significant variation in the medial rectus muscle insertion site in infantile esotropia and that any measurement based on the insertion site is subject to this variation. The corneoscleral limbus is a more reliable reference point than the site of the muscle insertion for measuring medial rectus muscle recessions in this condition. Future studies of the surgical treatment of infantile esotropia should include a measurement of the distance of medial rectus muscle recession from the corneoscleral limbus.

ACKNOWLEDGMENT

Nell Sedransk, Ph.D., of the University of Iowa, provided the statistical analysis of data.

References

1. Ing, M., Costenbader, F. D., Parks, M. M., and Albert, D. G.: Early surgery for congenital esotropia. Am. J. Ophthalmol. 61:1419, 1966.
2. Friendly, D. S.: Management of infantile esotropia. Int. Ophthalmol. Clin. 25:37, 1985.
3. Hiles, D. A., Watson, B. A., and Biglan, A. W.: Characteristics of infantile esotropia following early bimedial rectus recession. Arch. Ophthalmol. 98:697, 1980.
4. Parks, M. M., and Wheeler, M. B.: Concomitant esodeviations. In Duane, T. D. (ed): Clinical Ophthalmology, vol. 1. Philadelphia, J. B. Lippincott, 1988, ch. 12, pp. 1–4.
5. Hess, J. B., and Calhoun, J. H.: A new rationale for the management of large angle esotropia. J. Pediatr. Ophthalmol. Strabismus 16:345, 1979.
6. Szmyd, S. M., Nelson, L. B., Calhoun, J. H., and Spratt, C.: Large bimedial rectus recessions in congenital esotropia. Br. J. Ophthalmol. 69:271, 1985.
7. Apt, L., and Call, B. N.: An anatomical reevaluation of rectus muscle insertions. Ophthalmic Surg. 13:108, 1982.
8. Kushner, B. J., Preslan, M. W., and Vrabec, M.: Artifacts of measuring during strabismus surgery. J. Pediatr. Ophthalmol. Strabismus 24:159, 1987.
9. Apt, L.: An anatomical reevaluation of rectus muscle insertion. Trans. Am. Ophthalmol. Soc. 178:365, 1980.

OPHTHALMIC MINIATURE

I am living proof that the waters of Loveless Lake are potable because I swallowed half the lake every summer while waterskiing with my cousins. Once I struck the surface of the lake with such force that my right eyelid was rolled up into my head in a funny way. My cousin Simon told me I had lost my eyelid—and my cousin Hester added that the lost eyelid would lead to blindness. But Uncle Alfred managed to locate the missing eyelid, after a few anxious minutes.

John Irving, *A Prayer for Owen Meany*
New York, William Morrow and Company, Inc., 1989, p. 84

Subepidermal Calcified Nodules of the Eyelid

Andrew P. Ferry, M.D.

Two children had subepidermal calcified nodules of the upper eyelid. The first patient was a 13-year-old girl who noted painless increase in size of a lesion involving her right upper eyelid over four months. The clinical diagnosis was "warty papilloma." The second patient was a 13-year-old boy who had a slowly growing, keratinized lesion involving his left upper eyelid. The clinical diagnosis was "cutaneous horn." On histopathologic examination, the nodules demonstrated the characteristic changes associated with subepidermal calcified nodules, including the presence of calcified material in the uppermost dermis, occasional foreign body giant cells around the calcific masses, acanthosis of the overlying epithelium, and calcium granules in the epidermis.

Although subepidermal calcified nodules are well known to dermatologists and dermatopathologists, and although the skin of the head and neck (including the eyelid) is a site of predilection, most ophthalmologists and many ophthalmic pathologists are not familiar with these lesions.

Most affected individuals are children or adolescents. These lesions are not associated with disorders of calcium metabolism or with other systemic disease.

Two children (13 years old each) had subepidermal calcified nodules of the upper eyelid that exhibited the characteristic clinical and pathologic features of this benign disorder.

Accepted for publication Sept. 22, 1989.

From the Department of Ophthalmology, Medical College of Virginia, Virginia Commonwealth University, Richmond, Virginia. This study was presented at the Annual Meeting of the Verhoeff Society, Boston, Massachusetts, April 14, 1989. This study was supported in part by grants from the Dr. Berkeley H. Martin, Jr. Endowment Fund in Ophthalmology and Research to Prevent Blindness, Inc.

Reprint requests to Andrew P. Ferry, M.D., Department of Ophthalmology, Medical College of Virginia, Virginia Commonwealth University, Richmond, VA 23298.

Case Reports

Case 1

A 13-year-old black girl was examined by a pediatrician because of a "knot" that had been present in the skin of her right upper eyelid for approximately four months, which had increased slowly in size. There was no history of pain or of injury to the eyelid. The pediatrician regarded the lesion as an epithelial cyst and referred the patient to an ophthalmologist. On ophthalmologic examination, the lesion measured about 3 × 3 mm and was said to have a cystic quality. There was no associated erythema. The clinical diagnosis was "warty papilloma."

In initial planes of section, the lesion bore a superficial resemblance to a cyst (Fig. 1). A prominent mass of calcified material was present in the outer layers of the dermis. The overlying epidermis was hyperkeratotic and acanthotic, extending well into the dermis and partially enveloping the central calcified mass. The subepidermal calcium consisted of both finely granular forms and larger fragmented shards. Alizarin red and von Kossa stains were strongly positive, confirming the impression that the ma-

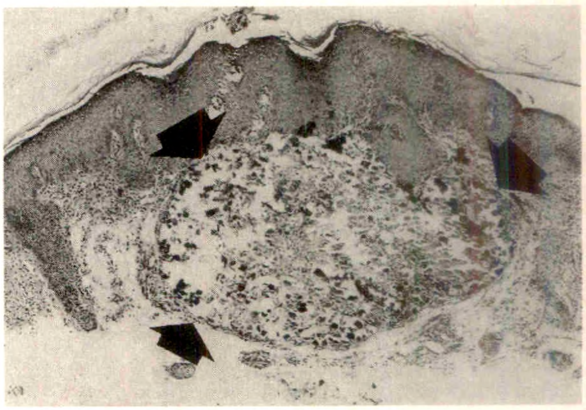


Fig. 1 (Ferry). Case 1. In initial plane of section, the lesion (arrowheads) bears a superficial resemblance to a cyst (hematoxylin and eosin, × 56).

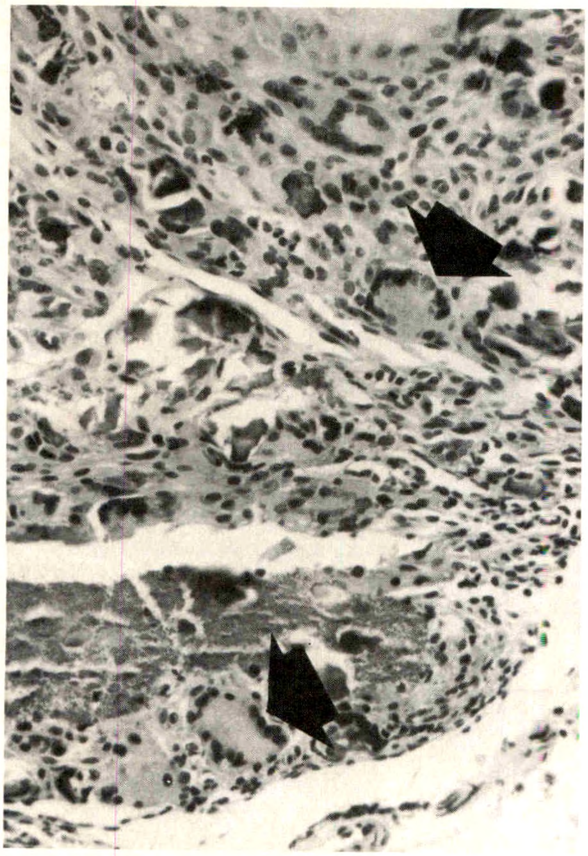


Fig. 2 (Ferry). Case 1. The stromal inflammatory cell infiltrate contains foreign body giant cells (arrowheads). A prominent accumulation of finely granular calcium is present immediately above the giant cell (arrow) near the bottom of the field. A small portion of epidermis appears at the top of the field (hematoxylin and eosin, × 250).

terial that was deeply basophilic in hematoxylin and eosin-stained sections was calcium. Interspersed between the calcified material were conspicuous collections of richly cellular connective tissue containing prominent foci of inflammatory cells, including scattered collections of foreign body giant cells (Fig. 2) and a few eosinophils.

In sections obtained from a deeper part of the lesion, the acanthosis and hyperkeratosis of the overlying epithelium were even more striking (Fig. 3). Prominent collections of fine calcium granules were present in all layers of the epidermis, having eroded from the underlying dermis so that in some areas they protruded from the external surface of the skin.

A light infiltrate of chronic inflammatory cells, primarily lymphocytes, was present in the dermis surrounding the calcified nodule. Neither

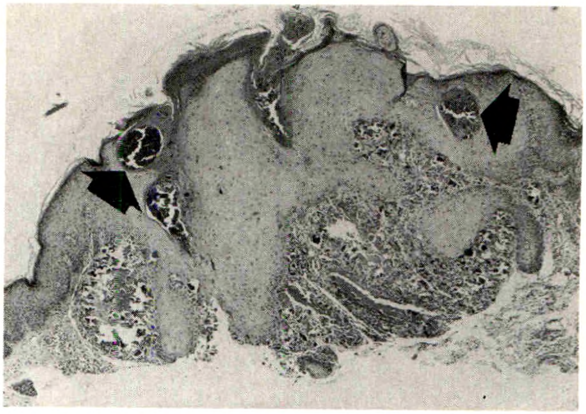


Fig. 3 (Ferry). Case 1. On sectioning deeper in the paraffin block, acanthosis and hyperkeratosis of the overlying epidermis are even more striking. Dense accumulations of calcium (arrowheads) approach the surface of the skin (hematoxylin and eosin, × 44).

nevus cells nor sweat glands were identifiable components of the lesion.

Case 2

A 13-year-old black boy was examined because of a growth on his left upper eyelid, which had been present for about a year and had slowly increased in size. His ophthalmologist described it as a beige, keratinized lesion measuring about 3.5 × 4 × 4 mm. The clinical diagnosis was "cutaneous horn."

The epidermis overlying the subepidermal nodule was acanthotic and hyperkeratotic (Fig. 4). The dermis was almost completely replaced by dense accumulations of calcium in both a finely granular form and in larger fragmented shards. The calcium deposits were strongly positive when subjected to alizarin red and von Kossa staining. Richly cellular connective tissue existed between the calcium deposits. As in Patient 1, there were prominent foci of inflammatory cells, including scattered collections of foreign body giant cells (Fig. 5) and a few eosinophils.

Discussion

Accounts of subepidermal calcified nodules of the eyelid are rare. There is a brief mention and illustration of a lesion (under the heading of "calcinosis cutis") in a review of 398 pediatric eyelid lesions.[1] Two papers on subepidermal calcified nodules have appeared in European ophthalmologic periodicals: the first in French

Fig. 4 (Ferry). Case 2. The striking hyperkeratosis (arrowheads) at the lesion's dome accounts for the clinical diagnosis of cutaneous horn. The dermis contains extensive accumulations of calcium, which occurs in both a finely granular form and larger fragmented shards (hematoxylin and eosin, × 25).

by Dhermy in 1970,[2] and the second in German by Blodi and Bersons in 1983.[3]

Winer[4] is credited with the first report of calcified subepidermal nodule, although, retrospectively, other cases have been traced back to at least 1927.[5] The eyelid was not involved in the three infants who were the subject of Winer's report. Winer considered the lesions to be congenital, a concept that is no longer tenable because many cases have since been reported in which the nodules developed from a previously normal site.

In 1963, Woods and Kellaway[5] reported 20 cases. In 18 cases, the lesion was solitary. Thirteen patients were male. In all but four cases, the nodules appeared in childhood or adolescence. Most of the nodules were located on the head (six on the external ear, six on the cheek, two on the nose, one on the chin, and one on the eyelid).

The second case of subepidermal calcified nodule of the eyelid was reported by Dhermy[2] in 1970. The patient was a 12-year-old boy who

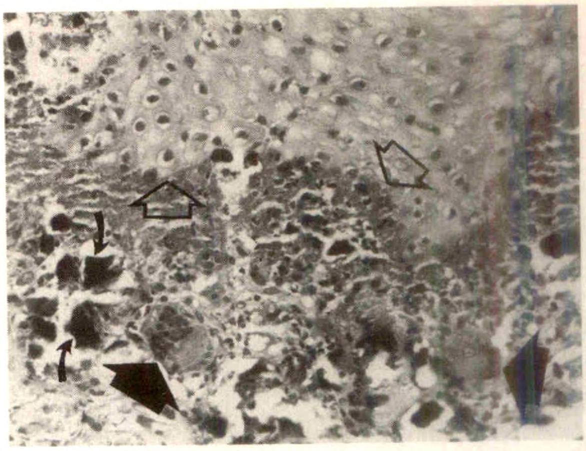


Fig. 5 (Ferry). Case 2. Beneath the eroded inner aspect of the epidermis (open arrowheads), the dermis contains prominent accumulations of calcific material, which occurs in both a finely granular form and as larger fragmented shards (curved arrows). Several giant cells (solid arrowheads) are present in the lower portion of the field (hematoxylin and eosin, × 250).

had a small tumor on the left upper eyelid. The clinical diagnosis was "papilloma."

In 1980, Tezuka[6] reported subepidermal calcified nodules in 11 patients seen between 1974 and 1980. Tezuka reported (personal communication, April 10, 1989) that he has seen an additional nine cases of subepidermal calcified nodules since the appearance of his publication in 1980. Of the 20 patients he studied, 11 were female and nine were male. Ages ranged from 4 to 78 years, with a mean age of 24.5 years. Two of the 20 patients had lesions that did not affect the ocular adnexa. In the remaining 18 patients, involvement of the ocular adnexa was as follows: lower eyelid in 12; upper eyelid in nine; and inner canthus in two. Three of the 18 patients whose ocular adnexa were affected had multiple lesions.

The fourth report of eyelid involvement in subepidermal calcified nodules was published by Blodi and Bersons[3] in 1983. They described one case from their laboratory and four cases from other institutions. Their patients ranged in age from 15 to 21 years. All of the patients were male. The nodules involved the upper eyelid in four patients and the medial canthus in one patient. In none of their patients was the correct diagnosis made preoperatively.

Among the clinical features of subepidermal calcified nodules are their predilection to occur in young individuals and their propensity to involve the skin of exposed areas, particularly that of the head and neck. The lesions are

usually warty or mamillated, but are sometimes smooth and domed. The diameter is typically from 3 to 10 mm. Most often the nodule is solitary, but they may be multiple. Most of them are white or yellow-white, and in some individuals a faint red halo surrounds the nodule. On palpation, the lesions are firm or hard and are located very superficially in the skin. Pain and irritation are not features of this disorder.

The correct diagnosis was not made preoperatively in the two patients described here, in Dhermy's patient, or in the five patients described by Blodi and Bersons. The preoperative diagnoses in these eight patients were as follows: papilloma in four; wart in two; xanthoma in one; and cutaneous horn in one. (Woods and Kellaway did not record the preoperative diagnosis for their patient.)

Only among the cases reported by Tezuka[6] has the correct diagnosis been made preoperatively. The preoperative clinical diagnosis in 18 patients who had involvement of the ocular adnexa was as follows: cutaneous calculus (subepidermal calcified nodule) in 14; hypertrophic scar in one; xanthoma tuberosum in one; syringoma in one; and molluscum contagiosum in one (personal communication, T. Tezuka, M.D., April 10, 1989).

On histopathologic examination, subepidermal calcified nodules characteristically demonstrate the presence of calcified material in the uppermost dermis, a few foreign body giant cells around the calcific masses, acanthosis of the overlying epithelium, and calcium granules in the epidermis. As was seen particularly in Case 1 of this study, the calcium in the epidermis may protrude from the surface of the skin, exemplifying the transepidermal elimination of calcium.[7] Electron microscopic examination has disclosed electron-dense, needle-shaped crystals in the cytoplasm of vacuolated cells. These crystals were shown to contain a large amount of calcium by x-ray microanalysis.[6] There was some evidence that the calcified material was associated with the intracellular granules of depleted mast cells.

The cause and pathogenesis of subepidermal calcified nodules are unknown but have been speculated on by other investigators. Origins that have been suggested for these lesions include the following: circumscribed fat necrosis in a xanthoma; calcification of a melanocytic nevus; and calcification of a sweat gland hamartoma. The evidence for all of these theories is unconvincing. The term currently used for these lesions is a descriptive one rather than one based on histogenetic origin.

References

1. Doxanas, M. T., Green, W. R., Arentsen, J. J., and Elsas, F. J.: Lid lesions of childhood. A histopathologic survey at the Wilmer Institute (1923-1974). J. Pediatr. Ophthalmol. 13:7, 1976.

2. Dhermy, P.: Calcification cutanée solitaire type Winer dans sa localisation palpébrale. Arch. Ophtalmol. 30:791, 1970.

3. Blodi, F. C., and Bersons, J. U.: Calcinose des augenlids. Klin. Monatsbl. Augenheilkd. 182:68, 1983.

4. Winer, L. H.: Solitary congenital nodular calcification of the skin. Arch. Dermatol. Syphilol. 66:204, 1953.

5. Woods, B., and Kellaway, T. D.: Cutaneous calculi. Subepidermal calcified nodules. Br. J. Dermatol. 75:1, 1963.

6. Tezuka, T.: Cutaneous calculus. Its pathogenesis. Dermatologica 161:191, 1980.

7. Eng, A. M., and Mandrea, E.: Perforating calcinosis cutis presenting as milia. J. Cutan. Pathol. 8:247, 1981.

OPHTHALMIC MINIATURE

Qwilleran had just experienced the first forkful of chicken livers rolled in bacon and seasoned with a touch of basil, and he rolled his eyes gratefully heavenward. In doing so, he caught the gaze of Kao K'o-Kung, perched on the refrigerator. The cat slowly and deliberately closed one eye in an unmistakable wink.

Lillian Jackson Braun, *The Cat Who Could Read Backwards*
Jove Books, New York, 1966, p. 77

AMERICAN JOURNAL OF OPHTHALMOLOGY®

FRANK W. NEWELL, *Publisher and Editor-in-Chief*
Suite 1415, 435 North Michigan Ave., Chicago, Illinois 60611

Published monthly by the OPHTHALMIC PUBLISHING COMPANY
Suite 1415, 435 North Michigan Avenue, Chicago, Illinois 60611

Directors

David Shoch, *President*
Edward W. D. Norton, *Vice President*
Frank W. Newell, *Secretary and Treasurer*
Bruce E. Spivey
Bradley R. Straatsma

EDITORIAL

Variations in Patient Care to Identify Preferred Management

Alfred Sommer

The cost and promise of new medical technology and increased expectations and utilization by the public have resulted in dramatic increases in the cost of health care, both in absolute dollars and as a share of the gross national product. Almost every country has been forced to reshape and manipulate its health care system in an attempt to improve access while controlling costs. Famous western examples include the British National Health Service and the more mixed Canadian system, which relies heavily on expenditure targets. These have often achieved increased patient access for urgent conditions, queues for elective surgery (two to three years for cataract extraction in the United Kingdom), and a lower living standard for most ophthalmologists.

Until recently, the thrust of health policy in the United States was to increase access to health care, primarily through health assistance to the poor (Medicaid) and the aged (Medicare). It will come as no surprise that the government has now decided to focus on the rising costs of health care. The problem they face is in deciding how and what to cut without doing damage to the quality of care or provoking public displeasure.

Health care regulators have two options: reduce reimbursement for each instance of medical service; or curtail the use of medical services, particularly those that are the most costly. They have already begun to move aggressively on the first front, establishing diagnosis-related groups and more recently the Physician's Payment Review Commission with its declared intention of adjusting, capping, and otherwise revising and reducing existing fee structures and controlling their future rise. It is generally assumed this will have a measurable but limited impact. Upward pressures on health expenditure are driven more by increased utilization of ever more costly technology, than by the rise in physician reimbursement for each procedure performed.

With rare exception, government agencies (and third-party payers who follow their lead)

have not yet seriously interfered with a physician's ability to do what the physician believes is in the best interests of the patient. That will change. Recent health services research has provided ample evidence that physicians do not always do what is in the best interests of their patients, and that these decisions have fiscal and quality of care implications.

John Wennberg of Dartmouth, the "father" of "small area variation," continues to provide the most compelling evidence.[1] Even within a single state (Maine) and among populations with similar demographic characteristics and access to health care, the risk of tonsillectomy, prostatectomy, hysterectomy, and other procedures varied markedly.[2,3] In some communities patients were five to 15 times more likely to undergo tonsillectomy than in others.[4] Surely, he reasoned, not everyone could be receiving the most appropriate care: the range of tonsillectomy rates was simply too large.

The point has been proven. In a splendid example of noncoercive education, Maine physicians organized the Maine Medical Assessment Program[3] to provide feedback to practicing physicians and an opportunity for those from high- and low-rate areas to compare and discuss indications for surgery. In this and other instances variation in surgical rates narrowed markedly, primarily by a dramatic, voluntary reduction in high-rate areas.[2,3] While the new rates were not necessarily correct in any absolute sense, they at least reflected the thoughtful consensus and combined wisdom of those treating the same condition.

The second line of evidence comes from appropriateness studies conducted by the Rand Corporation, largely under the guidance of Dr. Robert Brook. These exhaustive, exhausting, and expensive undertakings utilize panels of nationally acknowledged experts to review large series of cases as, for example, coronary bypass surgery. They decide, through a formalized consensus process, which were appropriate and which were not. In one series of carotid endarterectomies at least 25% were considered to have been inappropriate.[5]

Armed with this evidence, government regulators are determined to begin controlling costs at their source: not only by eliminating surgery that is clearly unnecessary, but by reimbursing only those practices and procedures deemed most appropriate and (cost) effective for that condition. Rather than leave this important process solely in the hands of the government bureaucracy, most specialty societies, including the American Academy of Ophthalmology, have constituted their own expert panels to establish practice guidelines.[6,7] Given the lack of solid data upon which to base many of these recommendations, some early decisions are unlikely to stand the test of time. Investigators are, however, developing a variety of new approaches for gathering needed data and for formulating appropriate policy.

The Patient Outcome Assessment Research Project represents the most ambitious government-sponsored initiative to date. Announced on Sept. 7, 1989, by Louis W. Sullivan, M.D., Secretary of Health and Human Services, this congressionally mandated activity is directly financed from the Medicare Trust Fund. By correlating variations in patient management with observed outcome, it seeks to develop a more appropriate basis for decision making than present evidence allows.[8] A variety of mechanisms would then be employed to identify and communicate preferred practices to relevant physicians. The process of data collection and analysis does not require physicians to change what they do; instead it seeks to capitalize on existing practice variations to identify, in a realistic and valid manner, those activities associated with better outcomes (and lower costs), as determined by clinical factors and patient satisfaction.

The first phase of this new initiative establishes four centers nationwide, each to study a different clinical condition. These include the management of acute myocardial infarction (Harvard), low back pain (University of Washington), and benign prostatic hypertrophy (Dartmouth). A multidisciplinary team from the Wilmer Institute (Drs. Alfred Sommer, James Tielsch, and Jonathan Javitt) and the Department of Health Services Research (Drs. Earl Steinberg, Marilyn Bergner, Jonathan Weiner, and Gerald Anderson, among others) at Johns Hopkins will study cataract, which is the only ophthalmic entity among the more than 100 conditions the National Center for Health Services Research was interested in having addressed. Data will come from literature reviews, analysis of specially compiled Medicare files, and most importantly, from the practices of collaborating ophthalmologists. A National Advisory Committee of ophthalmologists, which is expected to grow as additional expertise and interests are required, has been assembled to guide the Hopkins process (Drs. David Apple, Donald Doughman, Thomas Harbin, Harry Knopf, Stephen Obstbaum, Denis O'Day, Walter Stark, Arlo Terry, and C. P. Wilkinson). The exercise, expected to last at least five years, should help all of us better understand which approaches and procedures are most effective;

and provide valuable tools in the future for assessing management of other ocular conditions.

The process will not be simple, easy, or free of controversy. Outcome assessment should, however, provide a more rational basis for government and provider decisions than presently exists. As those decisions will impact on us all and particularly on the health of our patients, it is imperative that they be based, as soon as possible, on the strongest possible data.

Reprint requests to Alfred Sommer, M.D., Dana Center for Preventive Ophthalmology, Wilmer 120, Johns Hopkins Hospital, 600 N. Wolfe St., Baltimore, MD 21205.

References

1. Wennberg, J. E., and Gittelsohn, A.: Variations in medical care among small areas. Sci. Am. 246:120, 1982.

2. Wennberg, J. E., Blowers, L., Parker, R., and Gittelsohn, A.: Changes in tonsillectomy rates associated with feedback and review. Pediatrics 59:821, 1977.

3. Confronting Regional Variation: The Maine Approach. Chicago, Department of Health Care Review, Division of Health Policy and Program Evaluation, American Medical Association, 1986.

4. Wennberg, J. E., McPherson, K., and Caper, P.: Will payment based on diagnosis-related groups control hospital costs? N. Engl. J. Med. 311:295, 1984.

5. Merrick, N., Brook, R. H., Fink, A., and Solomon, D. H.: Use of carotid endarterectomy in five California Veterans Administration Medical Centers. JAMA 77:187, 1987.

6. Leape, L.: Unnecessary surgery. Pew Memorial Trust Policy Synthesis: 7. Health Serv. Res. 24:351, 1989.

7. Sommer, A., Weiner, J., and Gamble, L.: Developing specialty-wide standards of practice. The experience of ophthalmology. Qual. Rev. Bull. In press.

8. Greenfield, S.: The state of outcome research. Are we on target? N. Engl. J. Med. 320:1142, 1989.

LETTERS TO THE JOURNAL

Human Immunodeficiency Virus Seroprevalence Among Potential Corneal Donors From Medical Examiner Cases

David G. Hwang, M.D.,
Donald E. Ward, B.A.,
Melvin D. Trousdale, Ph.D.,
and Ronald E. Smith, M.D.

Department of Ophthalmology (D.G.H., M.D.T., R.E.S.), University of Southern California School of Medicine, and Lions Doheny Eye Bank (D.E.W., R.E.S.), Doheny Eye Institute.

Inquiries to Ronald E. Smith, M.D., Department of Ophthalmology, University of Southern California School of Medicine, Doheny Eye Institute, 1355 San Pablo St., Los Angeles, CA 90033.

The advent of routine screening of all potential corneal donors for a history of human immunodeficiency virus risk factors and for the presence of HIV antibody has greatly reduced but not eliminated the risk of HIV transmission. Several recent reports have documented rare occurrences of HIV transmission through transfusion of HIV antibody-screened blood products.[1] HIV-infected donors who are not detected by antibody testing include seropositive donors who test falsely negative, recently infected donors who have not yet seroconverted, and HIV-infected donors who remain persistently antibody-negative. In 1987, the rate of HIV antibody detection failure among first-time blood donors was estimated to range between 0.0005% and 0.002%, assuming a seroprevalence among first-time blood donors of 0.04%.[1]

The risk of HIV transmission through antibody-negative but virus-positive tissue increases in direct proportion to the prevalence of donor seropositivity. Accurate determination of seroprevalence in a given donor population is therefore essential for estimating the risk of transplantation-associated HIV transmission. The Centers for Disease Control estimated a range of 0.4% to 0.6% HIV seroprevalence among the general United States population in 1988.[2] A study conducted in Houston in 1986 reported a seropositivity rate of 0.3% among 1,517 consecutive corneal donors who had no known HIV risk factors.[3] Although the proportion of donors derived from medical examiner cases was not specified in the Houston study, a more recent report has suggested a higher HIV seroprevalence among medical examiner cases. Between May 1985 and February 1986, a 2.4% HIV seroprevalence was found among 205 Dallas medical examiner cases without known HIV risk factors.[4]

We reviewed 4,451 consecutive potential tissue donors from Los Angeles County Medical Examiner cases collected between March 1, 1986, and May 31, 1989 to determine HIV seroprevalence in the medical examiner donor population. A total of 1,680 potential donors (37.7%) were excluded on the basis of either known history of risk factors for HIV infection (according to the Centers for Disease Control criteria) or physical evidence of HIV-risk behavior (for example, needle tracks). These potential donors did not undergo HIV antibody screening. Of the remaining 2,771 potential donors, 27 (0.97%) were subsequently excluded based on testing repeatedly positive for HIV antibody by enzyme immunoassay. This rate of

HIV seropositivity among medical examiner cases was less than half the seroprevalence rate reported from Dallas.

Screening of medical examiner cases for historical or physical evidence of HIV risk factors was an effective first step in eliminating a substantial proportion of HIV-infected cases as potential donors. The seroprevalence of approximately 1.0% among screened donors was lower than the 1.6% rate of HIV seropositivity confirmed by Western blot analysis among consecutive unselected Los Angeles County Medical Examiner cases in 1988. At a seroprevalence rate of 1.0% and with an estimated 99% test sensitivity for HIV antibody screening by enzyme immunoassay, the risk of transplanting tissue from HIV-infected but antibody-negative donors is 0.01%. The risk of actual HIV seroconversion from corneal transplantation is probably much lower. No instances of HIV seroconversion after corneal transplantation have yet been noted despite at least seven reported cases of transplantation of corneal tissue from seropositive donors.[5]

Careful screening of medical examiner cases for historical or physical evidence of HIV risk factors is a valuable supplement to HIV antibody testing to minimize the risk of transplantation of HIV-infected corneas. Medical examiner cases undergoing such screening measures presently have a low rate of HIV seropositivity and can continue to serve as a valuable and safe source of surgical quality corneal tissue.

References

1. Ward, J. W., Holmberg, S. D., Allen, J. R., Cohn, D. L., Critchley, S. E., Kleinman, S. H., Lenes, B. A., Ravenholt, O., Davis, J. R., Quinn, M. G., and Jaffe, H. W.: Transmission of human immunodeficiency virus (HIV) by blood transfusions screened as negative for HIV antibody. N. Engl. J. Med. 318:473, 1988.

2. Karon, J. M., Dondero, T. J., Jr., and Curran, J. W.: The projected incidence of AIDS and estimated prevalence of HIV infection in the United States. J. Acquir. Immune Defic. Syndr. 1:542, 1988.

3. Wilhelmus, K. R., and Farge, E. J.: HIV antibody screening of corneal donors. Ophthalmologica 195:57, 1987.

4. Heck, E., Petty, C., Palestine, A., Luckenbach, M., Salahuddin, S. Z., Nussenblatt, R., Harris, W., Baxter, C., and McCulley, J.: ELISA HIV testing and viral culture in the screening of corneal tissue for transplant from medical examiner cases. Cornea 8:77, 1989.

5. O'Day, D. M.: Diseases potentially transmitted through corneal transplantation. Ophthalmology 96:1133, 1989.

Interferon Treatment of Herpetic Keratitis in a Patient With Acquired Immunodeficiency Syndrome

William McLeish, M.D.,
Stephen C. Pflugfelder, M.D.,
Cecelia Crouse, Ph.D.,
Stephen Rabinowitz, M.D.,
Darlene Miller, M.S.,
Edgar L. Hill, Ph.D,
and Sally Atherton, Ph.D.

Departments of Ophthalmology (W.McL., S.C.P., C.C., S.R., D.M., S.A.) and Microbiology-Immunology (C.C., S.A.), University of Miami School of Medicine, and Wellcome Research Laboratories (E.L.H.). Supported in part by Public Health Service Research Grants EY08193, EY021180, and EY06012.

Inquiries to Stephen C. Pflugfelder, M.D., Bascom Palmer Eye Institute, P.O. Box 016880, Miami, FL 33101.

Erlich and associates[1] recently reported the largest series (12 cases) of mucocutaneous herpes simplex virus type 2 infections in patients with acquired immunodeficiency who were unresponsive to oral acyclovir. The lack of treatment response in their cases was attributed to resistance of the isolates to acyclovir based on in vitro sensitivity testing. The following case report suggests that suppressed host immune defenses may play a significant role in the clinical unresponsiveness of herpes simplex viral infections in AIDS.

A 15-year-old girl with AIDS was seen in March 1988. She had a dendritic epithelial keratitis in her left eye. Total T-helper cell lymphocyte count at this time was 312/mm^3. The keratitis completely resolved with 1% trifluridine eyedrops. Dendritic epithelial keratitis then developed in the right eye in October 1988. The total T-helper cell lymphocyte count had decreased to 62/mm^3. Acyclovir (4 g orally/day) was started, and continued throughout the treatment period. Several topical antiviral agents including trifluridine 1% and idoxuridine 0.1% solutions, and vidarabine 3% ointment in recommended doses for periods of one to three weeks each were also used. Despite this therapy, the lesion assumed a geographic configuration, and increased in size to encompass

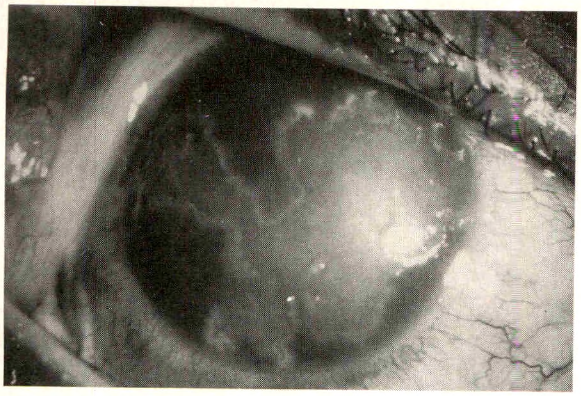


Fig. 1 (McLeish and associates). Herpes simplex virus type 1 geographic epithelial keratitis immediately before initiation of topical interferon.

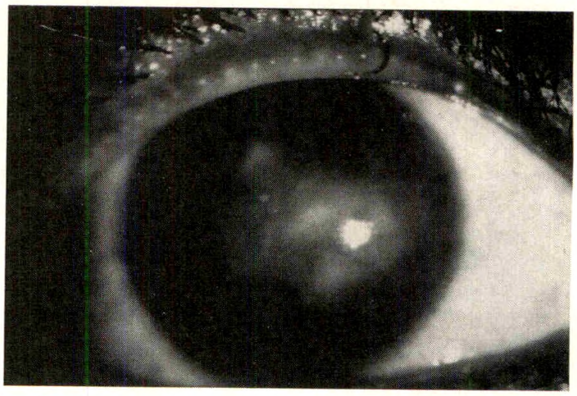


Fig. 2 (McLeish and associates). Complete resolution of epithelial keratitis after three weeks of topical interferon-alpha therapy.

over 80% of the cornea (Fig. 1). On Jan. 29, 1989, all antiviral agents were stopped, and topical recombinant interferon-alpha 2a was begun (one 12 x 10^6 units/ml twice daily). The epithelial keratitis completely resolved within three weeks (Fig. 2). Herpes simplex virus type 1 was cultured from corneal scrapings, performed on Dec. 1 and 29, 1988, and was also detected by polymerase chain reaction[2] of the scraped corneal epithelial cells by using primers and probes to a conserved region of the herpes simplex type 1 genome. In vitro sensitivity values were determined for both isolates to a variety of antiviral compounds by the dye-uptake method in Vero cells.[3] Compared to the herpes simplex type 1 functional type control strain (KOS), the two clinical isolates had similar 50% inhibitory concentration values for idoxuridine, vidarabine, and phosphonoformate. However, the 50% inhibitory concentration values of the clinical isolates were greater than the herpes simplex type 1 functional type control strain for antivirals requiring phosphorylation by thymidine kinase-acyclovir (16 times greater) and thymidine arabinoside (28 times greater).

The initial episode of herpetic keratitis in our patient was successfully treated with topical antiviral therapy. Subsequent infection displayed clinical resistance to multiple antiviral agents. Unlike the cases of Erlich and associates,[1] which showed in vitro resistance to acyclovir, the only agent used for therapy, our patient was treated with several different antiviral agents to which the isolates were sensitive in vitro. A concurrent decrease in total T-helper cell lymphocyte count was noted during the interval between the first and second infections in our patient. Treatment with alpha (leukocyte) interferon, an endogenously produced antiviral glycoprotein previously documented to be decreased in AIDS patients,[4] led to rapid resolution of the infection. Interferon treatment in our patient was initiated based on the previously demonstrated efficacy of topical interferon-alpha in the treatment of herpetic keratitis in immunocompetent individuals.[5] Our case suggests that lack of treatment response to virostatic antiviral drugs in immunocompromised individuals may be related to insufficient host viral defenses of which interferon-alpha may be an important component. This agent deserves further clinical investigation in these patients.

References

1. Erlich, K. S., Mills, J., Chatis, P., Mertz, G. J., Busch, D. F., Follansbee, S. E., Grant, R. M., and Crumpacker, C. S.: Acyclovir resistant herpes simplex virus infections in patients with the acquired immunodeficiency syndrome. N. Engl. J. Med. 320:293, 1989.

2. Ou, C. H., Kwok, S., Mitchell, S. W., Mack, D. H., Sninsky, J. J., Krebs, J. W., Feorino, P., Warfield, D., and Schochetman, T.: DNA amplification for direct detection of HIV-1 in DNA of peripheral blood mononuclear cells. Science 239:295, 1988.

3. McLauren, C., Ellis, M. N., and Hunter, G. A.: A colorimetric assay for measurement of the sensitivity of herpes simplex viruses to antiviral agents. Antiviral Res. 3:223, 1983.

4. Cesario, T., Yousefi, S., Carandang, G., and Tilles, J.: Interferon use during other virus infections. In Baron, S., Dianzani, F., Stanton, G. J., and Fleischmann, W. R. (eds.): The Interferon System. A

Current Review to 1987. Austin, Texas, University of Texas Press, 1987, pp. 447–452.
5. Sundmacher, R., Mattes, A., Neumann-Haefelin, D., Adolf, G., and Kruss, B.: The potency of interferon-alpha 2 and interferon-gamma in a combination therapy of dendritic keratitis. A controlled clinical study. Current Eye Res. 6:273, 1987.

Herpes Simplex Virus and Persistent Epithelial Defects After Penetrating Keratoplasty

Craig F. Beyer, D.O., Thomas J. Byrd, M.D., James M. Hill, Ph.D., and Herbert E. Kaufman, M.D.

Department of Ophthalmology, Louisiana State University School of Medicine. This study was supported in part by United States Public Health Service grants EY06114, EY06311, EY02672, and core grant EY02377 from the National Eye Institute.

Inquiries to James M. Hill, Ph.D., LSU Eye Center, 2020 Gravier St., Suite B, New Orleans, LA 70112-2234.

A persistent epithelial defect in the donor cornea after penetrating keratoplasty poses a serious threat to graft survival. We believe that herpes simplex virus may play a role in retarding epithelial healing after penetrating keratoplasty. Surgical decompression of the trigeminal nerve root reactivates latent herpes simplex virus in humans,[1] and surgical trauma from penetrating keratoplasty, in conjunction with postoperative corticosteroids, reactivates latent herpes simplex virus type 1 infection in rabbits.[2-4] Because the majority of the population carries herpes simplex virus in a latent phase,[5] reactivation after penetrating keratoplasty may occur, yet be unrecognized. We treated a patient with no history of herpes simplex virus stomatitis, labialis, genitalis, or keratitis who developed a herpes simplex virus epithelial defect in the donor cornea immediately after penetrating keratoplasty.

A 70-year-old man was seen at the Louisiana State University Eye Center on Aug. 14, 1989. The patient had undergone a penetrating keratoplasty for pseudophakic bullous keratopathy with anterior vitrectomy and intraocular lens exchange in December 1986. The graft gradually decompensated with a corneal thickness of 0.68 mm and corneal stromal and epithelial edema. The anterior chamber appeared quiet with a Simcoe style anterior chamber intraocular lens. Peripheral anterior synechiae and pupillary capture of the lens were apparent.

On Aug. 22, the patient underwent repeat penetrating keratoplasty with removal of the lens and lysis of the anterior synechiae. A posterior chamber lens was sutured through the sclera into the ciliary sulcus, and a pupilloplasty was performed. Methylprednisolone acetate (80 mg) was injected subconjunctivally, and a collagen shield soaked in gentamicin sulfate was placed on the cornea. Ocular cultures were obtained the day before the operation, as well as on the first, second, sixth, and 15th postoperative days. On the first postoperative day, the graft was clear, the anterior chamber demonstrated the usual amount of postoperative inflammation, and an epithelial defect was apparent. The patient was given prednisolone acetate, gentamicin, and cyclopentolate hydrochloride drops with dexamethasone sodium phosphate ointment at bedtime. On the sixth postoperative day, the epithelial defect was unchanged. It was approximately 4 mm wide, extending from the 3 o'clock to the 9 o'clock meridian of the donor-recipient interface. The defect was not characteristic of herpes simplex virus infection. There were no dendritic edges, although the two ocular cultures obtained that day were positive for herpes simplex virus. On Sept. 6, approximately two weeks after the operation, the defect had healed only slightly (Figure). A bandage lens was fitted, and the patient was given trifluridine eyedrops with

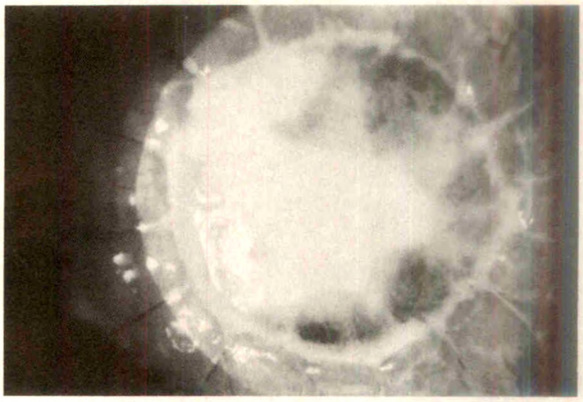


Figure (Beyer and associates). Epithelial defect two weeks after the operation. Fluorescein staining pattern (white area in donor cornea represents epithelial defect with fluorescein stain) was not suggestive of herpes simplex virus, yet previous herpes simplex virus cultures were positive.

a rapid taper of the prednisolone acetate. Cultures taken that day were negative. On the 27th postoperative day, the epithelial defect was almost completely healed. Six weeks after the operation, the epithelium was intact. One week later, a large epithelial defect caused by a tight bandage soft contact lens was observed. Nine weeks postoperatively, the defect was small and resolving. Cultures for herpes simplex virus taken at the six, seven, eight, and nine week visits were negative.

This case documents herpes simplex virus keratitis in a patient with the preoperative diagnosis of pseudophakic bullous keratopathy and no history of herpes simplex virus infections. The epithelial defect was not characteristic of herpes simplex virus infection, even though positive herpes simplex virus ocular cultures were obtained. Penetrating keratoplasty and postoperative corticosteroids reactivate latent herpes simplex virus infection in rabbits. Our case suggests that the same may occur in humans. Multiple cultures are necessary during the first ten postoperative days to detect herpes simplex virus infection, because a single negative culture may be a false negative.[4]

References

1. Pazin, G. J., Ho, M., and Jannetta, P. J.: Reactivation of herpes simplex virus after decompression of the trigeminal nerve root. J. Infect. Dis. 138:405, 1978.
2. Beyer, C. F., Arens, M. Q., Hill, G. A., Rose, B. T., Beyer, L. R., and Schanzlin, D. J.: Oral acyclovir reduces the incidence of recurrent herpes simplex keratitis in rabbits after penetrating keratoplasty. Arch. Ophthalmol. 107:1200, 1989.
3. Rose, B. T., Beyer, C. F., Arens, M. Q., Hill, G. A., Katsev, D. A., and Schanzlin, D. J.: Recurrent herpetic keratitis following penetrating keratoplasty in rabbits. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1988, p. 453.
4. Portnoy, S. L., Beyer, C. F., Hill, J. M., and Kaufman, H. E.: Coincidence of epithelial ulceration with positive HSV-1 ocular cultures after experimental autograft penetrating keratoplasty. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1989, p. 275.
5. Baringer, J. R., and Swoveland, P.: Recovery of herpes simplex virus from human trigeminal ganglia. N. Engl. J. Med. 288:648, 1973.

Neisseria cinerea Acute Purulent Conjunctivitis

Yue-Kong Au, M.D.,
Mark D. Reynolds, M.D.,
Ellen D. Rambin, M.S.,
and Salah B. Mahjoub, M.D.

Department of Ophthalmology, Louisiana State University Medical Center.

Inquiries to Yue-Kong Au, M.D., Department of Ophthalmology, LSU Medical Center, 1501 Kings Highway, Box 33932, Shreveport, LA 71130.

A 46-year-old man had a three-day history of red eyes and purulent discharge. The patient also had dysuria and a brown urethral discharge for seven days. Initial best-corrected visual acuity was R.E.: 20/200 and L.E.: 20/80. Findings included a right preauricular node, eyelid edema, bilateral conjunctival hyperemia and chemosis, copious purulent discharge, and bilateral scattered subepithelial corneal infiltrates (Fig. 1). Medical history was unremarkable. A Gram stain of the ocular discharge showed numerous gram-negative intracellular and extracellular diplococci (Fig. 2). The patient was admitted to the hospital and treated with intravenous ceftriaxone for presumed *Neisseria gonorrhoeae* conjunctivitis.

The organism was identified by plating the ocular discharge on chocolate and blood agar. The blood agar yielded only a few colonies of coagulase-negative staphylococci. The chocolate agar grew numerous gray colonies of gram-negative diplococci that were cytochrome oxidase and catalase positive. The isolate was subcultured in various media. In 24 hours, it

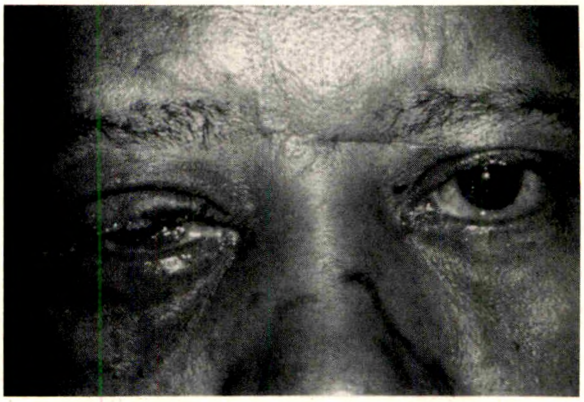


Fig. 1 (Au and associates). Acute bilateral purulent conjunctivitis caused by *N. cinerea* conjunctivitis.

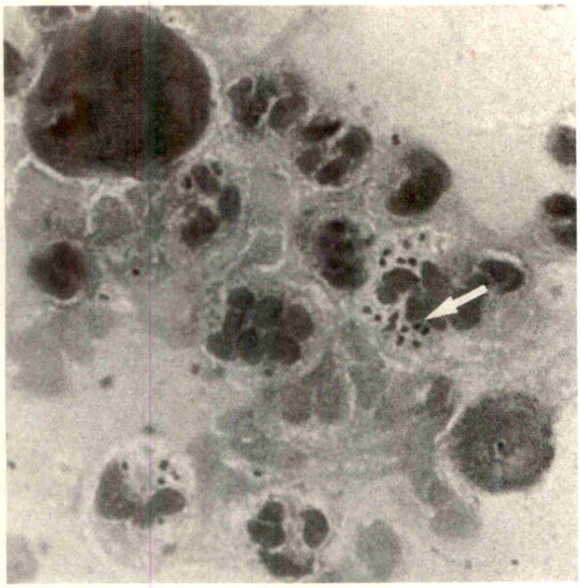


Fig. 2 (Au and associates). Gram stain of ocular discharge showing numerous intracellular gram-negative diplococci (arrow).

grew on chocolate and Mueller-Hinton agar but not on modified Thayer-Martin agar. The isolate also failed to ferment glucose, sucrose, and maltose. This organism is differentiated from *N. gonorrhoeae*, which grows on modified Thayer-Martin agar and does not ferment glucose.[1-3] Vitek's *Neisseria* Haemophilus identification card (Vitek Products, Hazelwood, Mo.) also identified the organism as *N. cinerea* with a 95% confidence level. The organism isolated did not produce β-lactamase. Urethral discharge was plated onto modified Thayer-Martin medium intended to isolate *N. gonorrhoeae*. Unfortunately, this medium does not support proper growth of *N. cinerea*, and no growth of any organism was detected. Results of laboratory tests for chlamydia, syphilis, and acquired immunodeficiency syndrome were all negative.

In the hospital, the patient received intravenous ceftriaxone, 1 g daily for seven days, and oral tetracycline, 250 mg four times daily, for possible concurrent chlamydial infection. Visual acuity recovered to R.E.: 20/30 and L.E.: 20/20. The patient improved greatly and was subsequently discharged.

Neisseria cinerea is considered a saprophytic bacterium found in many mucosas.[1,4,5] It has been isolated from normal conjunctiva,[2] but has not been shown to cause any ocular infection. This case of *N. cinerea* conjunctivitis emphasizes the ocular pathogenicity of this opportunistic organism.

References

1. Knapp, J. S., Totten, P. A., Mulks, M. H., and Minshew, B. H.: Characterization of *Neisseria cinerea*, a nonpathogenic species isolated on Martin-Lewis medium selective for pathogenic *Neisseria* species. J. Clin. Microbiol. 19:63, 1984.
2. Boyce, J. M., and Mitchell, E. B., Jr.: Difficulties in differentiating *Neisseria cinerea* from *Neisseria gonorrhoeae* in rapid systems used for identifying pathogenic *Neisseria* species. J. Clin. Microbiol. 22:731, 1985.
3. Boyce, J. M., Mitchell, E. B., Jr., Knapp, J. S., and Buttke, T. M.: Production of ^{14}C-labeled gas in Bactec *Neisseria* differentiation kits by *Neisseria cinerea*. J. Clin. Microbiol. 22:416, 1985.
4. Wax, L.: The identity of *Neisseria* other than the gonococcus from the genito-urinary tract. J. Venerol. Dis. Inf. 31:208, 1950.
5. Berger, U., and Paepcke, E.: Untersuchungen uber die asaccharolytischen Neisserien des menschlichen Nasopharynx. Z. Hyg. 148:269, 1962.

Persistent Corneal Defect Caused by *Listeria monocytogenes*

Richard A. Eiferman, M.D., Kevin T. Flaherty, M.D., and Arthur K. Rivard, M.D.

Department of Ophthalmology and Visual Sciences, University of Louisville.

Inquiries to Richard A. Eiferman, M.D., Department of Ophthalmology and Visual Sciences, University of Louisville, School of Medicine, Kentucky Lions Eye Research Institute, 301 E. Muhammad Ali Blvd., Louisville, KY 40292.

Listeria monocytogenes is an uncommon corneal pathogen capable of penetrating an intact corneal epithelium. The organism usually affects immunocompromised patients and neonates.

We treated a 69-year-old man with a history of chronic alcohol abuse and a five-day history of an irritated right eye. Initial examination disclosed an irregular central epithelial defect. The patient was initially treated with dilation, antibiotic ointment, and patching. The epitheli-

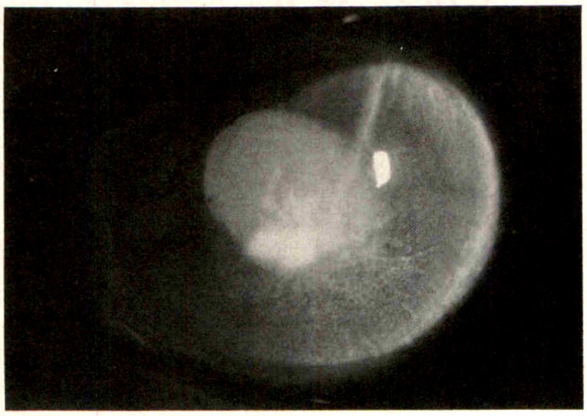


Fig. 1 (Eiferman, Flaherty, and Rivard). Trophic epithelial defect and punctate keratitis.

um, however, continued to heal partially and slough for ten days (Fig. 1). The patient then developed a 1- to 2-mm hypopyon with an endothelial fibrin plaque and corneal infiltrates (Fig. 2). Corneal cultures and scrapings showed gram-positive rods. The smear was initially interpreted as diphtheroids until *L. monocytogenes* was isolated. The eye healed uneventfully with topical gentamicin sulfate and a temporary tarsorrhaphy.

Listeria monocytogenes is a rare cause of keratitis. It has been previously reported to cause a necrotizing ring ulcer,[1] plastic iritis,[2] and endophthalmitis.[3] Our case demonstrates that *L. monocytogenes* can also manifest as a persistent epithelial defect in immunocompromised patients. This organism should be considered when a recurrent defect is out of proportion to the anterior chamber reaction. The finding of gram-positive rods should not be immediately dismissed as a contaminant.

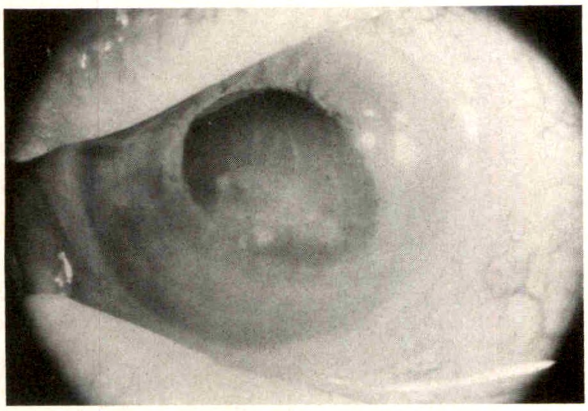


Fig. 2 (Eiferman, Flaherty, and Rivard). Healed defect with superficial corneal infiltrates and hypopyon.

References

1. Holbach, L. M., Bialasiewicz, A. A., and Boltze, H. J.: Necrotizing ring ulcer of the cornea caused by exogenous *Listeria monocytogenes* serotype IV b infection. Am. J. Ophthalmol. 106:105, 1988.
2. Holland, S., Alfonso, E., Gelender, H., Heidemann, D., Mendelsohn, A., Ullman, S., and Miller, D.: Corneal ulcer due to *Listeria monocytogenes*. Cornea 6:144, 1987.
3. Beuchat, L., Hirachel, B., Tabatabay, C., and Filthuth, I.: Intraocular listeria. J. Fr. Ophtalmol. 8:797, 1985.

Dilution and Storage of Recombinant Tissue Plasminogen Activator (Activase) in Balanced Salt Solutions

Carole Ward, B.S., and Suzanne Weck, M.S.

Pharmaceutical Research and Development, Genentech, Inc.

Inquiries to Carole Ward, Genentech, Inc., 460 Pt. San Bruno Blvd., San Francisco, CA 94080.

Articles have been published recently concerning the use of recombinant tissue plasminogen activator in the treatment of postvitrectomy intraocular fibrin formation.[1,2] Doses of 25 μg of tissue plasminogen activator have been used in these studies. This is a small dose compared to the amount supplied in the commercially available product (Activase, 50- or 20-mg vial). In order to obtain the concentration of tissue plasminogen activator needed for clinical treatment, the investigators have reconstituted the product as directed to 1 mg/ml with sterile water for injection (United States Pharmacopeia) and then diluted this solution to 25 μg/100 μl with Balanced Salt Solution.[1] In some instances this solution has then been aliquoted and frozen for future use.

This procedure has raised certain concerns. Genentech recommends an eight-hour shelf life after reconstitution to 1 mg/ml with sterile water for injection (United States Pharmacopeia). Activase does not contain an antibacterial preservative and is only intended for single doses. The excipients present in the formula-

tion provide an excellent medium for bacterial growth, and, therefore, the procedure described in the articles may seriously compromise the sterility of the product. The formulation has been optimized to provide the balance of protein and excipients that will ensure the claimed efficacy, safety, and shelf life of the product when used as suggested by the package insert. Activase should only be diluted to 0.5 mg/ml with either 0.9% sodium chloride injection (United States Pharmacopeia) or 5% dextrose injection (United States Pharmacopeia). Dilution to 0.25 mg/ml with Balanced Salt Solution as recommended could potentially compromise the solubility of the protein, because the solubilizing effect of the excipients will also be diluted, possibly causing the protein to precipitate. Additionally, the calcium and magnesium salts present in the Balanced Salt Solution may react with the phosphate anion present in the tissue plasminogen activator preparation causing precipitation of insoluble calcium and magnesium phosphate salts.

Studies in our laboratories have indicated that precipitate formation occurs when tissue plasminogen activator is diluted to 0.25 mg/ml with Balanced Salt Solution and stored for 24 hours at room temperature. No precipitation was noted for placebo solutions diluted in the same manner. This suggests that the protein solubility has been compromised or an interaction between the protein and one or more of the excipients has occurred. If this dilution is stored at −20 C for 24 hours, the light scattering of these solutions is increased upon thawing, indicating that a change in the product has occurred.

Based on these considerations and the experimental results, Activase should not be diluted in Balanced Salt Solution and stored for any length of time at either room temperature or −20 C.

References

1. Williams, G. A., Lambrou, F. H., Jaffe, G. J., Snyder, R. W., Green, G. D J., Devenyi, R. G., and Abrams, G. W.: Treatment of post-vitrectomy fibrin formation with intraocular tissue plasminogen activator. Arch. Ophthalmol. 106:1055, 1988.

2. Ortiz, J. R., Walker, S. D., McManus, P. E., Martinez, L. A., Brown, R. H., and Jaffe, G. J.: Filtering bleb thrombolysis with tissue plasminogen activator. Am. J. Ophthalmol. 106:624, 1988.

Corticosteroid-Responsive Traumatic Optic Neuropathy

Byron L. Lam, M.D.,
and Thomas A. Weingeist, M.D.

Department of Ophthalmology, University of Iowa.
This study was supported in part by an unrestricted grant from Research to Prevent Blindness, Inc.

Inquiries to Byron L. Lam, M.D., Department of Ophthalmology, University of Iowa Hospitals and Clinics, Iowa City, IA 52242.

The efficacy of systemic corticosteroids in the treatment of traumatic optic neuropathy has not been proven because responses are often variable, and improvements may occur without treatment.[1,2] Recently, we evaluated a case of traumatic optic neuropathy with peripheral retinal injury that responded dramatically to corticosteroids. When the corticosteroid dosage was abruptly lowered, visual acuity decreased precipitously but improved quickly after corticosteroid treatment was reinstituted. We believe that our case demonstrates the potential utility of corticosteroid therapy in some cases of traumatic optic neuropathy.

An 18-year-old man was seen for sudden visual loss immediately after a pellet gun injury to the left orbit in April 1986. The left upper eyelid was ecchymotic, and an entrance wound

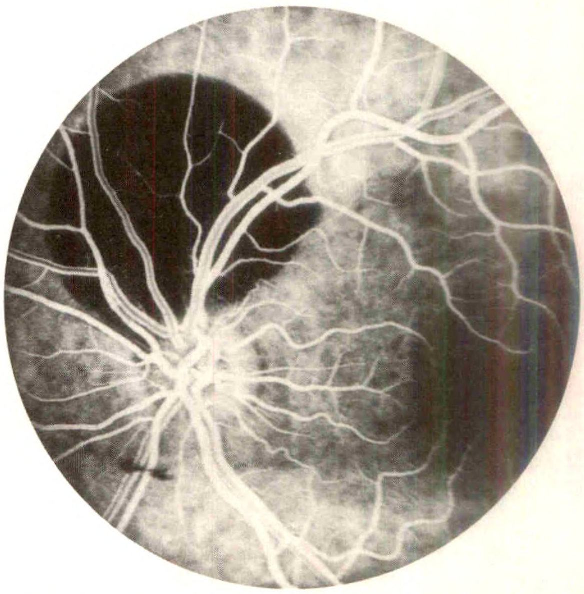


Fig. 1 (Lam and Weingeist). Fluorescein angiogram of the left eye showing round-shaped subretinal blood superior to the disk. The macula was spared of any direct injury.

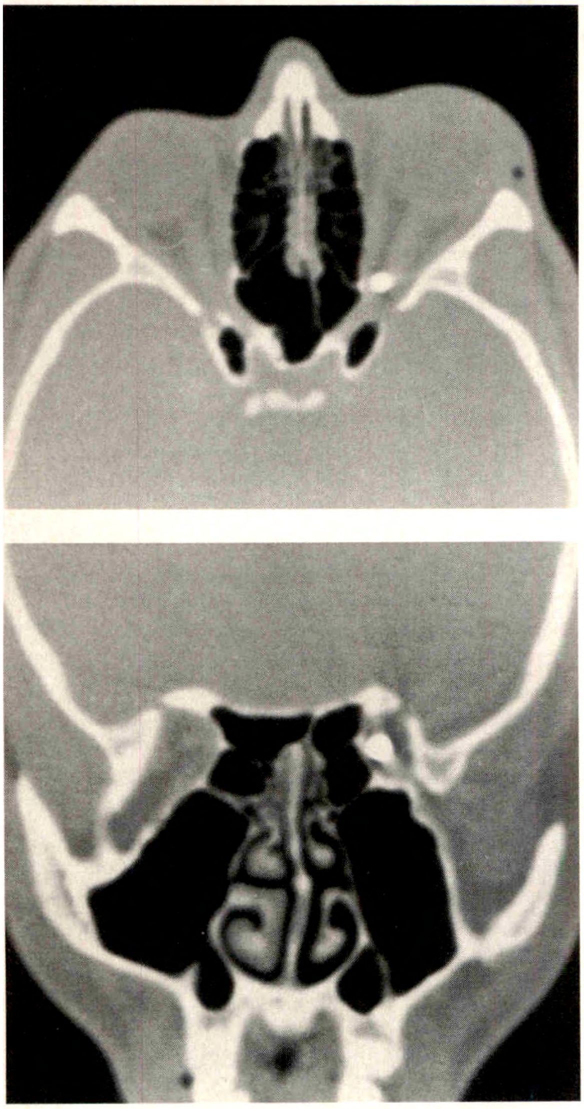


Fig. 2 (Lam and Weingeist). Computed tomography, axial view (top) and coronal view (bottom), of the orbits showing a foreign body at the left orbital apex, next to the optic nerve. Orbital echography showed no optic nerve compression.

was centered on the eyebrow. Visual acuity was R.E.: 20/20 and L.E.: 20/100. There was a relative afferent pupillary defect of 2.7 log units in the left eye. Intraocular pressures were R.E.: 15 mm Hg and L.E.: 17 mm Hg. The left eye had a clear anterior segment with some vitreous cells. The fundus showed diffuse Berlin's edema superiorly, round-shaped subretinal blood near the disk, and baring of the sclera with retinal necrosis peripherally at the 12 o'clock meridian (Fig. 1). Computed tomography showed a pellet at the left orbital apex, next to the optic nerve (Fig. 2). Traumatic optic neuropathy with blunt peripheral retinal injury was diagnosed. The patient was admitted and treated with cycloplegia, oral antibiotic, and intravenous dexamethasone (50 mg every six hours, then 25 mg every six hours).

The next day, visual acuity in the left eye improved to 20/30. The afferent pupillary defect remained, however, at 2.9 log units in the left eye. Color plates, Humphrey foveal thresholds, critical foveal flicker fusion, and the visual-evoked potential were all moderately worse in the left eye. Goldmann visual fields showed an inferotemporal quadrantanopic defect baring to the disk in the left eye. Orbital echography disclosed a foreign body in the left apex without nerve compression and a slightly thickened optic nerve. The blunt injury to the superior retina was demarcated with laser photocoagulation.

The patient improved, and the intravenous dexamethasone was tapered over the next three days from 25 mg every six hours to 15 mg every six hours. Four days after the injury, visual acuity in the left eye had improved to 20/20, and he was discharged on a regimen of oral prednisone, 100 mg daily.

One day after discharge, the patient returned and complained of progressive pain and deteriorating vision in the left eye. The patient had taken only 20 mg of prednisone that day. Visual acuity in the left eye had decreased to 20/300. The relative afferent pupillary defect in the left eye remained at 2.6 log units, and the fundus was unchanged. Echography showed increased subarachnoid fluid of the left optic nerve.

The patient was admitted and given intravenous dexamethasone (50 mg, then 30 mg every six hours). The next day, visual acuity in the left eye improved to 20/25, and the dexamethasone was tapered. Over the next five days, visual acuity in the left eye improved to 20/20, and the relative afferent pupillary defect in the left eye decreased to 1.7 log units. Color plates, central flicker fusion, and the visual-evoked potential remained moderately depressed in the left eye. Goldmann visual fields also did not improve. The patient was discharged on a regimen of oral prednisone, 80 mg daily, which was tapered over one month. The patient was followed up for six months, and visual acuity remained 20/20. The relative afferent pupillary defect in the left eye decreased to 1.1 log units.

The response to corticosteroids in this case of traumatic optic neuropathy was dramatic both initially and later when the patient was noncompliant. Although the patient recovered visual

acuity of 20/20, optic nerve tests still showed residual optic neuropathy. In addition, the large amount of relative afferent pupillary defect was out of proportion to the retinal injury and suggested a neuropathy.[3] Anderson, Panje, and Gross[4] have included a case in which a dramatic response to corticosteroids was also seen on two occasions, but the second decrease in vision occurred seven days after corticosteroids were discontinued and 24 hours after surgical facial fracture reduction. Based on our case, we believe that high doses of systemic corticosteroids may be helpful in some cases of traumatic optic neuropathy where subperiosteal hemorrhage[5] is not the cause of visual loss and where intracanalicular edema may be present. Administration of systemic corticosteroids should be considered in those patients with no contraindications.

References

1. Fujitani, T., Inoue, K., Takahashi, T., Ikushima, K., and Asai, T.: Indirect traumatic optic neuropathy. Visual outcome of operative and nonoperative cases. Jpn. J. Ophthalmol. 30:125, 1986.
2. Lessell, S.: Indirect optic nerve trauma. Arch. Ophthalmol. 107:382, 1989.
3. Folk, J. C., Thompson, H. S., Farmer, S. G., O'Gorman, T. W., and Dreyer, R. F.: Relative afferent pupillary defect in eyes with retinal detachment. Ophthalmic Surg. 18:757, 1987.
4. Anderson, R. J., Panje, W. R., and Gross, C. E.: Optic nerve blindness following blunt forehead trauma. Ophthalmology 89:445, 1982.
5. Wolter, J. R.: Subperiosteal hematomas of the orbit in young males. A serious complication of trauma or surgery in the eye region. Trans. Am. Ophthalmol. Soc. 77:104, 1979.

Ophthalmomyiasis in an Eyelid Reconstruction

Stephen L. Bosniak, M.D., and Jeffrey D. Schiller, M.D.

Department of Ophthalmic Plastic and Reconstructive Surgery, Manhattan Eye, Ear, and Throat Hospital.

Inquiries to Stephen L. Bosniak, M.D., 300 Central Park W., New York, NY 10024.

Myiasis is the invasion of human tissues by the larvae of dipterous insects. Ophthalmomyiasis of the ocular adnexa is rarely encountered in North America. We treated a patient for ophthalmomyiasis of a reconstructed eyelid.

A 63-year-old diabetic man taking 20 units of insulin isophane daily had a painlessly enlarging basal cell carcinoma of the left lower eyelid and cheek. After resection of the entire left lower eyelid and a large portion of the left cheek, primary reconstruction was performed, including a free tarsoconjunctival graft from the left upper eyelid, a semicircular cheek rotational flap, a medial forehead pedicle flap, and free supraclavicular skin graft. The sutures were removed after one week. Before the next scheduled visit, the patient came to the emergency room with multiple larvae, which infested the entire reconstructed area (Figure). Examination at that time showed duskiness of the edges of the cheek flap. The other grafts were intact and viable. Because the larval infestation involved the bed beneath the reconstructed area, the area was debrided and the grafts were removed. The area was allowed to granulate. The eye was treated with topical antibiotic ointment. A pretibial ulcer was also found to be infested with larvae.

Ophthalmomyiasis includes external, orbital, and internal types. External infestations involve the eyelids, conjunctiva, or both,[1] and can progress to orbital invasion.[2] Larval infestations tend to be progressive and invasive elsewhere in the body, but, with the exception of the internal ocular variety, they rarely invade the viscera.

Ulcerated skin lesions with devitalized tissue are preferred sites, but entry may be through insect bites in normal skin.[3,4] Conjunctival infestation may occur without predisposing ulcerations.[5] The occurrence may be obvious, with visible larvae, or may resemble a furuncle or cellulitis, which does not respond to antibiotic

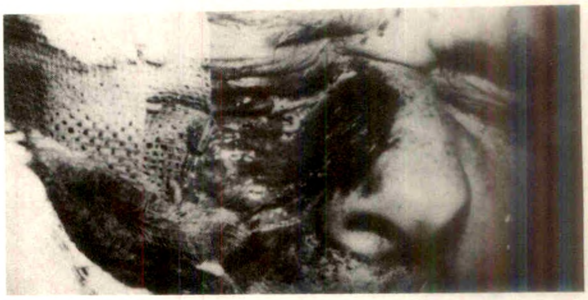


Figure (Bosniak and Schiller). A 63-year-old man with larval infestation of the reconstructed right lower eyelid and cheek.

therapy. Humans are not the preferred hosts of most dipterous insects. Human myiasis is considered an accidental infection rather than a facultative or obligatory one. Common hosts include horses, cattle, sheep, deer, rodents, and rabbits.

Because of the rarity of ophthalmomyiasis, few clinicians have any experience with treating this condition. These patients are treated by removing the larvae and controlling any secondary infection with antibiotics. A single or a few larvae can be removed by simple surgical excision. Aggressive resection may be necessary when the number of larvae is great or the infestation is invasive. Superficial infestations have been treated with a variety of solutions to paralyze, narcotize, or suffocate the larvae, including chloroform, ether, cocaine, turpentine, and petroleum jelly. Although rare, dermal ophthalmomyiasis can occur in normal or traumatized ocular adnexae. Treatment with local debridement may be adequate.

References

1. Hennessy, D. J., Sherrill, J. W., and Binder, P. S.: External ophthalmomyiasis caused by *Estrus ovis*. Am. J. Ophthalmol. 84:802, 1977.
2. Kersten, R. C., Shoukrey, N. M., and Tabbara, K. F.: Orbital myiasis. Ophthalmology 93:1228, 1986.
3. Cogen, M. S., Hays, S. J., and Dixon, J. M.: Cutaneous myiasis of the eyelid due to *Cuterebra* larva. JAMA 258:1795, 1987.
4. Rodrigues, M. M., Weiss, C. B., and Muncy, D. W.: Ophthalmomyiasis of the eyelid caused by *Cuterebra* larva. Am. J. Ophthalmol. 78:1024, 1974.
5. Mazzeo, V., Ercolani, E., Trombetti, D., Todeschini, R., and Gaiba, G.: External ophthalmomyiasis. Int. Ophthalmol. 11:73, 1987.

Linear Subcutaneous Fat Atrophy After a Single Corticosteroid Injection for Ocular Adnexal Hemangioma

Lois M. Townshend, M.D., and Edward G. Buckley, M.D.

Department of Pediatric Ophthalmology, Duke University Medical Center.

Inquiries to Edward G. Buckley, M.D., Department of Ophthalmology, Duke University Medical Center, Box 3802, Durham, NC 27810.

Since Kushner[1] first described subcutaneous, intralesional corticosteroid injection for treating infantile, periocular, capillary hemangiomas, several serious complications have been described. Local injections have been associated with eyelid necrosis,[2] central retinal artery occlusion,[3] and eyelid depigmentation.[4] Droste and associates[5] described two children who developed linear, subcutaneous fat atrophy after receiving three separate intralesional corticosteroid injections. We treated a patient who developed a similar pattern of subcutaneous fat atrophy after only one injection of intralesional corticosteroids.

A 3-month-old girl was examined for a right lower eyelid mass. The lesion was first noticed shortly after birth, as well as three similar lesions on the left arm and one on the right foot. The child was the product of a normal pregnancy and delivery, and she was otherwise healthy.

Examination showed a soft, compressible, blue lesion in the region of the right lower eyelid. Fixation pattern was central, steady, and maintained in both eyes. Ocular motility was full. Cycloplegic refraction was +1.50 sphere in each eye. Computed axial tomography showed a mass extending into the inferior orbit, not involving the intraconal space. Infantile capillary hemangioma was diagnosed, and we decided to observe the patient at intervals.

After several subsequent visits with no significant change in the hemangioma, the patient returned for follow-up at the age of 12 months. On this occasion, the hemangioma had enlarged and cycloplegic refraction disclosed 2

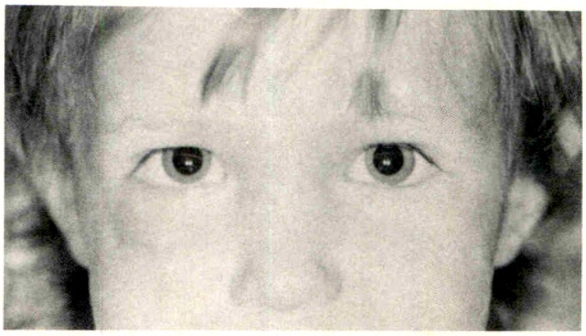


Fig. 1 (Townshend and Buckley). Subcutaneous fat atrophy two months after single intralesional repository corticosteroid injection.

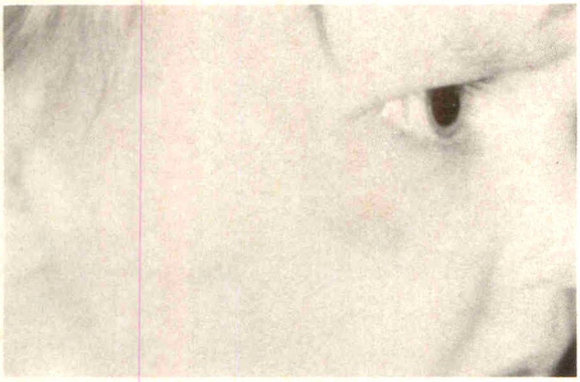


Fig. 2 (Townshend and Buckley). Fat atrophy in the region of the lower right lateral eyelid and linear atrophy extending from the right lateral canthus.

diopters of astigmatism along the 80-degree meridian in the affected right eye. A dosage of 1 ml of a 50% mixture of triamcinolone acetonide (40 mg/ml) and betamethasone sodium phosphate (6 mg/ml) was injected into the superficial portion of the hemangioma.

Two months after the intralesional injection, two subcutaneous linear depressions were noted which extended superiorly and inferiorly from the region of the lateral canthus. A larger area of depression was evident in the lateral lower eyelid at the initial injection site (Figs. 1 and 2). Four months after the intralesional injection, the atrophic areas remained unchanged.

Local fat atrophy resulting from repository corticosteroid injection has been well described in the pediatric and the rheumatology literature. Droste and associates reported a linear pattern of atrophy that seems to follow local lymphatic channels.[5] The first patient they described received three separate injections of triamcinolone acetonide and betamethasone sodium phosphate, with a total of 4 ml of solution. The second patient also received three similar injections with a total of 3 ml of solution. Subcutaneous fat atrophy occurred approximately 9 and 19 months respectively after the initial injection. Our patient developed subcutaneous fat atrophy after a single repository corticosteroid injection. Although the total amount of triamcinolone acetonide and betamethasone sodium phosphate solution was only 1 ml, this small amount of corticosteroid caused significant fat atrophy two months after the injection.

References

1. Kushner, B. J.: Local steroid therapy in adnexal hemangioma. Ann. Ophthalmol. 11:1005, 1979.
2. Sutula, F. C., and Glover, A. T.: Eyelid necrosis following intralesional corticosteroid injection for capillary hemangioma. Ophthalmic Surg. 18:103, 1987.
3. Shorr, N., and Seiff, S. R.: Central retinal artery occlusion associated with periocular corticosteroid injection for juvenile hemangioma. Ophthalmic Surg. 17:229, 1986.
4. Cogan, W. S., and Elsas, F. J.: Eyelid depigmentation following corticosteroid injection for infantile ocular adnexal hemangioma. J. Pediatr. Ophthalmol. Strabismus. 26:35, 1989.
5. Droste, P. J., Ellis, F. D., Sondhi, N., and Helveston, E. M.: Linear subcutaneous fat atrophy after corticosteroid injection of periocular hemangiomas. Am. J. Ophthalmol. 105:65, 1988.

Spontaneous Orbital Hemorrhage Associated With Idiopathic Inflammatory Pseudotumor

John V. Linberg, M.D., and Mark Mayle, M.S.

Department of Ophthalmology, West Virginia University School of Medicine.

Inquiries to John V. Linberg, M.D., Department of Ophthalmology, West Virginia University School of Medicine, Morgantown, WV 26506.

Idiopathic inflammatory pseudotumor of the orbit is more common in adults than children. Children, however, are more prone to recurrence after treatment.[1,2] The common clinical manifestations include pain, proptosis, motility disturbances, and conjunctival chemosis.[2] We treated a child with idiopathic inflammatory pseudotumor who developed a severe spontaneous retrobulbar hemorrhage that caused acute pain, proptosis, emesis, and visual loss.[3]

The patient, a 4-year-old boy, initially had a one-week history of left proptosis and periocular swelling (Fig. 1). The left eye had marked periocular inflammatory signs and reduced ocular motility. Laboratory values included an increased white blood cell count of 11,700 cells/mm^3, with lymphocytes (52%) and eosinophils (8%). A computed tomographic scan disclosed extraocu-

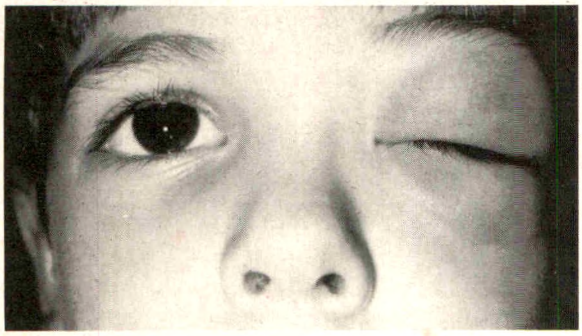


Fig. 1 (Linberg and Mayle). A 4-year-old boy had a one-week history of left proptosis, periocular edema, and diplopia.

lar muscle thickening and enhancement of the posterior sclera (Fig. 2).

The diagnosis of idiopathic inflammatory pseudotumor was based on clinical signs of acute inflammatory proptosis, computed tomographic evidence of enlarged extraocular muscles, and the presence of eosinophilia. This diagnosis was further confirmed by the patient's dramatic response to 30 mg daily of prednisone, resulting in the complete resolution of signs and symptoms within 48 hours. Attempts to taper the dosage of prednisone resulted in relapsing symptoms.

Repeat computed tomography obtained after ten weeks of treatment with oral corticosteroids showed resolution of extraocular muscle enlargement. No other abnormalities were present.

Four months after the initial occurrence, while on a regimen of 4 mg of prednisone daily, the patient was rushed to the clinic with signs of an acute retrobulbar hemorrhage. Clinical findings included severe left proptosis, eyelid ecchymosis, and loss of ocular motility. The parents indicated that these changes had developed over a period of five minutes. The intraocular pressure was greater than 100 mm Hg, and visual acuity was reduced to hand motions. Additional findings included a severe afferent pupillary defect, gray optic disk, and minimal perfusion of the retinal arteries. The child was lethargic and had emesis. Canthotomy and cantholysis failed to decrease intraocular pressure, and, therefore, the child was rushed to the operating room for orbital decompression. Intraocular pressure then returned to normal, optic disk perfusion was restored, and postoperative visual acuity was 20/20 with normal pupillary reactions.

Oral prednisone was tapered slowly over a period of six months. The child has not been given corticosteroids and has remained asymptomatic for three years. A recentmagnetic resonance image was carefully evaluated for signs of

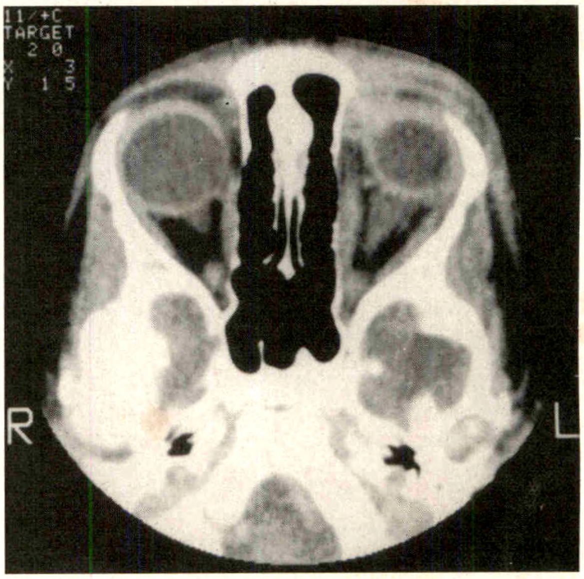


Fig. 2 (Linberg and Mayle). Axial computed tomography showing enlarged extraocular muscles, scleral enhancement, and irregular infiltrates in the fat of the left orbit.

lymphangioma, varix, tumor, or any cause of hemorrhage. The scan, however, was normal.

Spontaneous orbital hemorrhage has been reported in association with labor, hypertension, hemophilia, lymphangioma, varix, and even moderate physical exertion.[3,4] None of these factors can be implicated in our patient, who was playing quietly when the hemorrhage occurred.

Eyelid ecchymosis and moderate orbital hemorrhage have recently been reported in several adults with acute myositis.[5] Clinicians should be aware of this potential complication of idiopathic inflammatory pseudotumor.

References

1. Mottow, L. S., and Jakobiec, F. A.: Idiopathic inflammatory orbital pseudotumor in children. Arch. Ophthalmol. 96:1410, 1978.

2. Kennerdell, J. S., and Dresner, S. C.: The nonspecific orbital inflammatory syndromes. Surv. Ophthalmol. 29:93, 1984.

3. Krohel, G. B., and Wright, J. E.: Orbital hemorrhage. Am. J. Ophthalmol. 88:254, 1979.

4. Law, F. W.: Spontaneous orbital hemorrhage. Br. J. Ophthalmol. 55:556, 1971.

5. Reifler, D. M., Leder, D., and Rexford, T.: Orbital hemorrhage and eyelid ecchymosis in acute orbital myositis. Am. J. Ophthalmol. 107:111, 1989.

Ocular Flutter in Vidarabine Toxicity

Martin Gizzi, M.D., Steven Rudolph, M.D., and Anthony Perakis, M.D.

Department of Neurology, Mount Sinai School of Medicine, City University of New York.

Inquiries to Martin Gizzi, M.D., Department of Neurology, Mount Sinai Hospital, One Gustave L. Levy Pl., New York, NY 10029.

Saccadic ocular movements occurring in rapid sequence without an intersaccadic interval are referred to as ocular flutter if horizontal, or as opsoclonus if multidirectional. Saccadic oscillations are abnormal and are often accompanied by myoclonus and ataxia. Recent reviews by Digre[1] and Dropcho and Payne[2] enumerated the cases reported in adults. Associated conditions include infection, neuroblastoma, lung cancer, and metabolic disturbances. Metabolic disturbances include toxicity from amitriptyline, chlordecone, lithium with haloperidol, malathion, phenytoin with diazepam, thallium, and toluene.

Vidarabine (adenine arabinoside) is a purine nucleoside that impairs the early steps of viral DNA synthesis. It has antiviral activity against several of the herpesviruses and is used systemically in the treatment of severe herpes simplex and varicella-zoster infections. The central nervous system toxicity of this drug usually occurs in individuals with impaired renal function and typically includes confusion, tremor, and ataxia.[3] Permanent neurologic deficits are rare. We describe a patient who developed ocular flutter, tremor, and confusion after treatment of herpes simplex with vidarabine.

A 29-year-old woman with acquired immunodeficiency syndrome was admitted to Mount Sinai Hospital with severe genital herpes simplex infection and was treated with intravenous vidarabine (14 mg/kg daily). Six days after starting therapy with this agent she developed tremulousness, myoclonus, ataxia, and mild confusion. She was noted to have frequent bursts of ocular flutter. Her urea nitrogen blood level was 11 mg/dl and her creatinine blood level was 1.3 mg/dl. Spinal fluid analysis and a contrast-enhanced computed tomographic scan of the brain were normal. Vidarabine was discontinued. The following day, direct current electro-oculography showed frequent saccadic oscillations in the horizontal plane, particularly when the patient attempted voluntary ocular movements. The oscillations were seen equally often with the eyes open or closed. Two days after discontinuation of therapy, the saccadic oscillations and tremors diminished. Results of the patient's neurologic examination were normal the following day.

It is often difficult to ascribe a neurologic finding to a single etiologic factor in a patient with AIDS. Because the spinal fluid analysis and a computed tomographic scan of the brain were normal, it is unlikely that any infectious or neoplastic process could have caused this syndrome without progression to a more devastating form. Furthermore, the disappearance of the neurologic symptoms after cessation of treatment strongly implicates vidarabine as the causative agent.

Autopsy material from a case of vidarabine toxicity has demonstrated chromatolysis of neurons in the cerebral cortex, the basal ganglia, the thalamus, the brain stem, and the dentate nucleus of the cerebellum, with little or no reaction in the glia.[4] Diffuse neuronal chromatolysis without axonal damage is most likely indicative of metabolic injury.

References

1. Digre, K. B.: Opsoclonus in adults. Arch. Neurol. 43:1165, 1986.
2. Dropcho, E., and Payne, R.: Paraneoplastic opsoclonus-myoclonus. Association with medullary thyroid carcinoma and review of the literature. Arch. Neurol. 43:410, 1986.
3. Collignon, P. J., and Sorrell, T. C.: Neurological toxicity associated with vidarabine (adenine arabinoside) therapy. Aust. N.Z. J. Med. 13:627, 1983.
4. Van Etta, L., Brown, J., Mastri, A., and Wilson, T.: Fatal vidarabine toxicity in a patient with normal renal function. JAMA 246:1703, 1981.

Branch Retinal Artery Occlusion After Platelet Transfusion

Craig M. Greven, M.D., Erik van Rens, M.D., and M. Madison Slusher, M.D.

Department of Ophthalmology, Bowman Gray-Wake Forest University School of Medicine.

Inquiries to Craig M. Greven, M.D., Department of Ophthalmology, Bowman Gray-Wake Forest University School of Medicine, 300 S. Hawthorne Rd., Winston-Salem, NC 27103.

Occlusion of a retinal arteriole from an exogenous source leads to transient or permanent

visual dysfunction. Documented cases of exogenous emboli include talc in intravenous drug abusers[1] and corticosteroids after retrobulbar or intranasal injection.[2,3] We observed a branch retinal artery occlusion in a patient immediately after platelet transfusion for thrombocytopenia secondary to treatment of leukemia.

A 26-year-old man with a one-year history of acute myelogenous leukemia was undergoing intensification therapy with intravenous cytarabine. The patient became pancytopenic after therapy. White blood cell count was 220/mm^3, hemoglobin level was 9.5 mg/dl, and platelet count was 21,000/mm^3. The patient was given six units of platelets through a central venous line for the thrombocytopenia. Immediately after transfusion, the patient noted an inferotemporal paracentral scotoma in the left eye. The scotoma lasted 16 hours and then totally resolved. The day after transfusion, visual acuity was R.E.: 20/20 and L.E.: 20/20. No afferent pupillary defect was noted. Ophthalmoscopy of each eye showed venous engorgement and scattered dot and blot hemorrhages. The left fundus had retinal edema in the distribution of a branch retinal artery adjacent to the disk, supplying a portion of the papillomacular bundle (Fig. 1). No emboli could be seen. Intravenous fluorescein angiography confirmed delayed filling of the involved branch retinal artery (Fig. 2). Systemic examination including echocardiography failed to disclose an endogenous source of the emboli. Follow-up examination two weeks later showed resolution of the previous area of retinal edema.

Anemia and hyperviscosity have been used to explain the retinal vascular changes in acute leukemia.[4] The engorged retinal veins and scattered hemorrhages occurring in each eye of our patient probably reflect the pancytopenia. Our patient was not hypercoagulable, as evidenced by the pancytopenia and negative screen for disseminated intravascular coagulation.

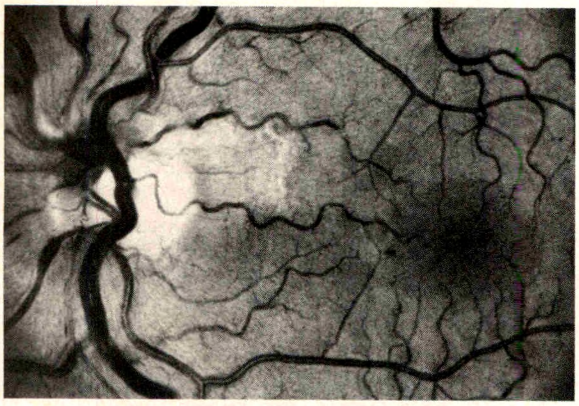


Fig. 1 (Greven, van Rens, and Slusher). Left eye showing retinal edema at superotemporal aspect of optic disk.

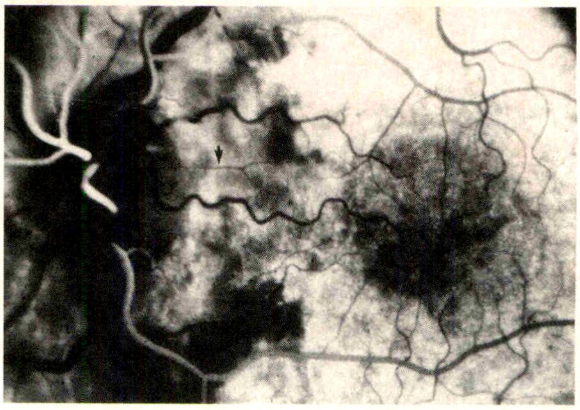


Fig. 2 (Greven, van Rens, and Slusher). Fluorescein angiogram of left eye showing retinal arterial filling and background choroidal fluorescence. Note the nonfilling of a branch retinal artery supplying the area of retinal edema, which suggests previous occlusion.

Talc emboli reach the retinal arterial circulation through pulmonary collateral vessels formed in response to long-term injections.[5] We believe that a platelet embolus reached our patient's arterial circulation through a pulmonary arteriovenous shunt vessel formed in response to a previous episode of cavitary pneumonia. It then reached the retinal circulation, resulting in a branch retinal artery obstruction. This complication must be considered in any patient with acute visual dysfunction after transfusion of blood products.

References

1. Kresca, L. J., Goldberg, M. F., and Jampol, L. M.: Talc emboli and retinal neovascularization in a drug abuser. Am. J. Ophthalmol. 87:334, 1979.
2. Ellis, P. P.: Occlusion of the central retinal artery after retrobulbar corticosteroid injection. Am. J. Ophthalmol. 85:352, 1978.
3. Whiteman, D. W., Rosen, D. A., and Pinkerton, R. M. H.: Retinal and choroidal microvascular embolism after intranasal corticosteroid injection. Am. J. Ophthalmol. 89:851, 1980.
4. Rosenthal, A. R.: Ocular manifestations of leukemia. Ophthalmology 90:899, 1983.
5. Gass, J. D. M.: Stereoscopic Atlas of Macular Diseases, ed. 3. St. Louis, C. V. Mosby, 1985, p. 350.

Laser Treatment of the Retinal Periphery With the +90-Diopter Lens

Elisha Bartov, M.D., and Giora Treister, M.D.

Goldschleger Eye Institute, Sheba Medical Center.

Inquiries to Elisha Bartov, M.D., Eye Department, Sheba Medical Center, Tel-Hashomer 52621, Israel.

We have introduced the use of the +90-diopter lens for biomicroscopy and laser treatment of peripheral, retinal lesions. We believe this use is an important improvement in controlling and accurately applying laser treatment through small pupils or media opacities. This new method is needed in situations where other currently used methods are deficient. The viewing quality with a plane prism, such as the Goldmann three-mirror lens, is dependent on pupil size and the clarity of the media of the eye. Indirect contact biomicroscopy systems, such as the Rodenstock Panfunduscope lens, the Mainster lens, or the +90-diopter lens attached to a contact lens,[1,2] allow wide-field view of the posterior pole and the midperiphery. Extreme eccentric gaze, however, tends to dislocate the contact lens from the cornea, which inhibits the treatment of peripheral lesions in many cases.

Noncontact indirect biomicroscopy systems, such as the +90 or the +60-diopter lenses, allow wide-field observation of the retinal periphery, even through a restricting viewing aperture. This is clinically important when attempting to view the retina through a small pupil or a small YAG laser capsulotomy. The presence of an intraocular lens makes viewing the periphery more difficult because of the severe astigmatism induced by the oblique view. In such cases, if the retinal lesions are extensive and broad, that is, extend significantly along the anteroposterior axis, treatment with a prism contact lens may be extremely difficult.

Using the +90-diopter lens in laser treatment is a simple extension of standard indirect noncontact biomicroscopy technique.[3] The area to be treated is brought into the field of view of the lens by directing the patient to gaze in the direction of the lesion. Since there is no contact lens involved, wide excursions of the direction of gaze are possible, allowing lesions near the ora serrata to be seen in the lens. Once the designated area of treatment is brought into view, the aiming beam is pointed toward it. Treatment is performed as indicated by the retinal disease. However, because the laser spot diameter on the retina is approximately 42% larger than the size indicated by the instrument, an appropriate adjustment of the spot size is necessary. Blinking and ocular movements are usually minor disturbances, and are no more disturbing than in the course of a usual examination session. We also found the use of the +90-diopter lens practical for laser treatment of the midperiphery, where it compares favorably with indirect contact biomicroscopy systems and in patients with painful or inflamed eyes, where the noncontact nature of the use of the +90-diopter lens is advantageous.

Ophthalmologists experienced with the diagnostic use of the +90-diopter lens will find its implementation for laser treatment an easy and extremely useful extension of their present skills.

References

1. Bartov, E., and Lewis, H.: New lens system for indirect fundus biomicroscopy. Am. J. Ophthalmol. 106:367, 1988.

2. Colebrander, A.: Principles of ophthalmoscopy. Contact lens for the indirect method. In Duane, T. D., and Jaeger, E. A. (eds.): Clinical Ophthalmology, chapter 63. Philadelphia, Harper & Row, 1979, pp. 20 and 21.

3. Lundberg, C.: Biomicroscopic examination of the ocular fundus with a +60-diopter lens. Am. J. Ophthalmol. 99:490, 1985.

A Simple Device to Standardize Measurements of Retinal Structures in Fundus Photographs and Retinal Angiograms

Carlos W. Arzabe, M.D., Alex E. Jalkh, M.D., Enrique Fariza, M.D., Jun Akiba, M.D., and Miguel A. Quiroz, M.D.

Retina Associates, Eye Research Institute, Massachusetts Eye and Ear Infirmary.

Inquiries to Alex E. Jalkh, M.D., Retina Associates, 100 Charles River Plaza, Boston, MA 02114.

Measurement of retinal vessel width and fundus lesions is important in the assessment and follow-up of some retinal diseases.[1-3] Investigators have used projected fundus images, cali-

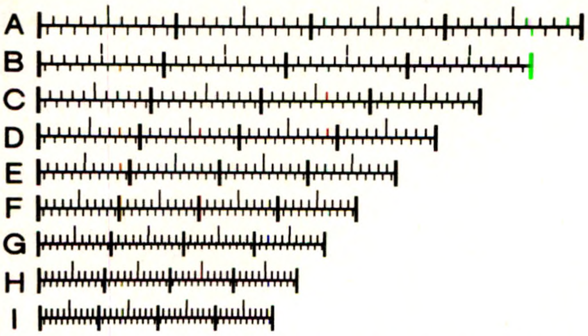


Fig. 1 (Arzabe and associates). Each large section in every horizontal line lettered A to I represents one disk diameter. Each smaller subdivision represents 1/20 of a disk diameter. This can be included in a 35-mm slide.

bers, densitometers, split-image measurements, and image-analysis algorithms to make these measurements. Most of these methods are difficult and not available for daily clinical use.

We use a standardized, simple, and fast technique to measure retinal lesions by means of fractions of disk diameters. The ruler is constructed through a computer program that allows scale manipulation to correct for the difference in magnification of fundus photographs and angiograms produced by different fundus cameras. Fundus cameras are constructed so that the magnification of the fundus is similar in different parts of the film plane.[4]

Measurements are based on the horizontal diameter of the optic disk in various photographic settings. The size of the optic nerve is constant for a given eye, and retinal lesions are measured as fractions of this horizontal diameter.

The ruler consists of horizontal lines lettered A to I, each 10% smaller than the previous (Fig. 1). This allows measurement of any optic disk diameter. Each line is divided into four sections that are then divided into 20 sections. The ruler, incorporated onto a 35-mm photographic transparency slide, is used by matching the horizontal diameter of the optic disk in a color photograph or fluorescein angiogram with the first large section of one of the horizontal lines on the ruler. This line is then used as a reference to measure different retinal lesions or distances in that eye in 1/20 fractions of a disk diameter (Fig. 2). When follow-up is necessary to evaluate enlargement of a retinal lesion, this device corrects the magnification between different fundus cameras and photographic sessions.[5] A loupe or a +20-diopter lens provides enough magnification for the daily clinical application of the ruler. The ruler can be copied by taking a 35-mm slide of Figure 1.

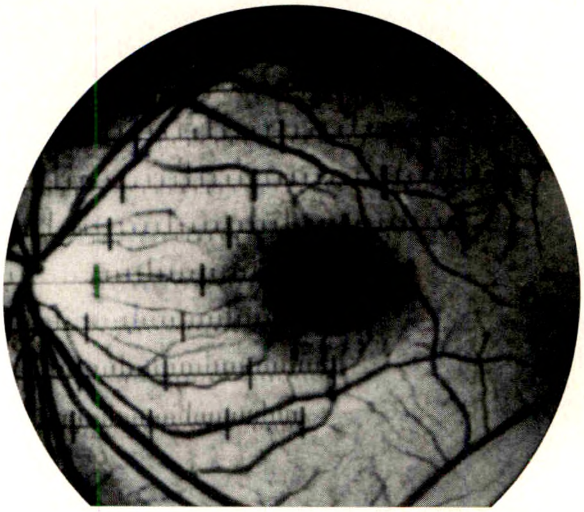


Fig. 2 (Arzabe and associates). Ruler being used by matching one of the large sections on a horizontal line of the ruler with the horizontal diameter of the optic disk.

References

1. Bracher, D., Dozzi, M., and Lotmar, W.: Measurement of vessel width on fundus photographs. Graefes Arch. Clin. Exp. Ophthalmol. 211:35, 1979.
2. Ward, P. N., Tomlinson, S., and Taylor, C. J.: Image analysis of fundus photographs. The detection and measurement of exudates associated with diabetic retinopathy. Ophthalmology 96:80, 1989.
3. Hodge, J. V., Parr, J. C., and Spears, G. F S.: Comparison of methods of measuring vessel widths on retinal photographs and the effect of fluorescein injection on apparent retinal vessels calibers. Am. J. Ophthalmol. 68:1060, 1969.
4. Leutwein, K., and Littmann, H.: The fundus camera. In Safir, A. (ed.): Refraction and Clinical Optics. New York, Harper & Row, 1980, p. 458.
5. Romano, P. E.: Simple photogrammertic diagnosis of optic nerve hypoplasia. Arch. Ophthalmol. 107:824, 1989.

Correspondence

Test-Retest Variability in Glaucomatous Visual Fields

EDITOR:

We read with interest the article, "Test-retest variability in glaucomatous visual fields" (Am. J. Ophthalmol. 108:130, August 1989) by A. Heijl, A. Lindgren, and G. Lindgren, and the clinically relevant commentary, "Interpreting automated perimetry" (Am. J. Ophthalmol. 108:189, August 1989) by D. A. Anderson. Using the Humphrey field analyzer, the authors show that intertest variability of a point in the visual field is related to the magnitude of the deviation from the age-corrected normal threshold for that point. What Heijl, Lindgren, and Lindgren have shown on the Humphrey perimeter, we have also shown on the Octopus perimeter.[1,2] Despite a difference in background illumination between the Octopus (4 apostilbs) and Humphrey (31.5 apostilbs) perimeters, intertest variability using the Octopus is similar to that found using the Humphrey. We plotted the mean threshold for each point in the visual field against its standard deviation for ten eyes with glaucoma (Figure). The mean threshold and its corresponding standard deviation were calculated for each test location across eight visual fields performed within one month using the Octopus perimeter program 32.

The Figure illustrates that as the threshold of a point decreases, its standard deviation across serial visual fields, and the intertest variability, increases. We found that intertest variability reaches a maximum when the mean sensitivity of a point falls between 2 and 14 dB. For these moderately to severely depressed points, the pointwise standard deviation across the eight visual fields ranges from 3 to 10 dB. Since all testing was performed within one month in stable glaucoma patients, such fluctuations represent intertest variability and not actual change. Visual field changes attributed to progressive glaucomatous disease must be in excess of expected fluctuations. Even if the threshold of a point is known, it is not known whether the variability falls at the lower end of the spectrum (S.D. = 3 dB) or the higher end (S.D. = 10 dB). Knowledge of the relationship between threshold and variability does not enable one to draw conclusions from two visual fields. Interpretation of visual field progression across a series of visual fields, however, may be greatly increased by incorporating the relationship between threshold and variability and the relationship between point location and variability into the analysis, as Heijl, Lindgren, and Lindgren note for mildly disturbed points.

We look forward to computer software that will incorporate this information into its analysis, but agree with Anderson's caveat of overreliance on computers. Since statistically significant change and clinically significant change do not always coincide, the need to manually analyze serial visual fields point by point will not be eliminated.

JODY R. PILTZ, M.D.
Vancouver, Canada
RICHARD J. STARITA, M.D.
Dallas, Texas

References

1. Piltz, J. R., Starita, R. J., Fechtner, R. D., and Twersky, Y.: Fluctuation of serial automated visual fields in glaucomatous and normal eyes. ARVO ab-

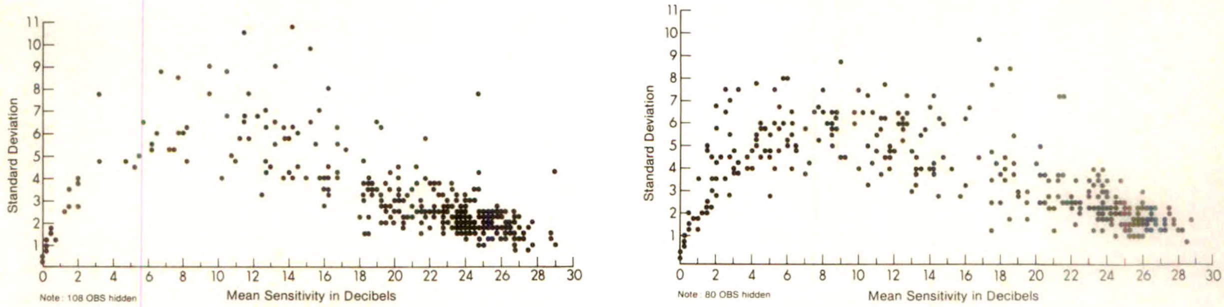


Figure (Piltz and Starita). Mean threshold sensitivity versus standard deviation for each point in the visual field. OBS = observations. Left, Right eyes. Right, Left eyes.

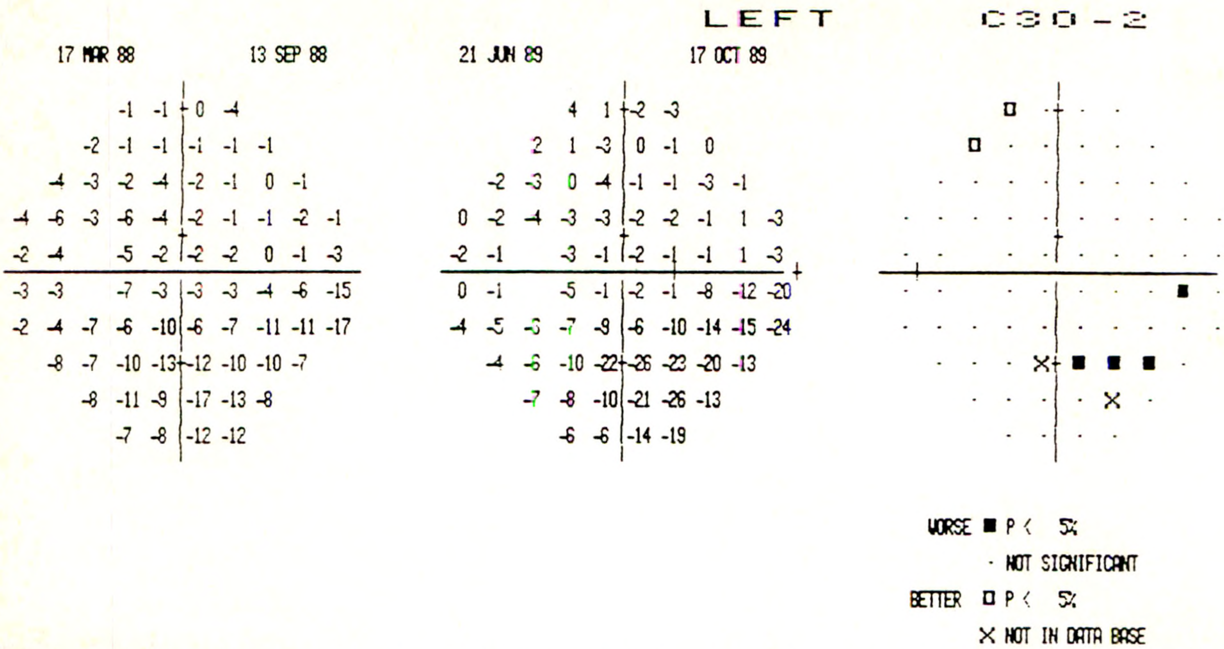


Figure (Heijl, Lindgren, and Lindgren). Change probability map printout from experimental software for the Humphrey perimeter. Left, Average pointwise deviations from age-normal values from two baseline tests (decibels). Center, Average pointwise deviations from two follow-up tests. Right, Change probability map indicating statistical worsening over time several points in the inferior nasal field, improvement in two superiorly.

stracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1986, p. 159.

2. Starita, R. J., Piltz, J. R., Lynn, J. R., and Fellman, R. L.: Total variance of serial Octopus visual fields in glaucomatous eyes. In Greve, E. L., Heijl, A. (eds.): Proceedings of the Seventh International Visual Field Symposium. Dordrecht, Martinus Nijhoff/ Dr. W. Junk Publishers, 1987, pp. 85–90.

Reply

EDITOR:

We were aware of the abstract and the article, cited by Drs. Piltz and Starita. Both communications report intertest static perimetric threshold variability in ten eyes of five glaucoma patients, in terms of the global indices long-term fluctuation (LF) and short-term fluctuation (SF). We were not aware, however, that the authors had also studied the dependence of pointwise variability as a function of point sensitivity, as we can now see in their previously unpublished figure. We are delighted to see that their results are in basic agreement with ours.

In contrast to Piltz and Starita, we were mainly interested in studying test-retest variability in individual locations in the visual field, and in determining the dependence of that variability on the degree of baseline abnormality. Because of the large physiologic variation of sensitivity with age and eccentricity, we found it necessary to use deviations from the age-corrected normal threshold values, instead of raw threshold values. We found that it was possible to define improved empiric prediction limits for pointwise threshold variability when both defect depth and eccentricity were taken into account.

We, too, appreciate the need for computer software to facilitate the analysis of the often complex fluctuations in series of glaucoma fields. We are presently testing such experimental software (Figure), that we hope may be added to a package for statistical analysis of Humphrey visual fields, which we have previously developed.[1]

ANDERS HEIJL
Malmö, Sweden
ANNA LINDGREN
GEORG LINDGREN
Lund, Sweden

Reference

1. Heijl, A., Lindgren, G., and Olsson, J.: A package for the statistical analysis of visual fields. Doc. Ophthalmol. Proc. Ser. 49:153, 1987.

Timolol-Pilocarpine Combined vs Timolol and Pilocarpine Given Separately

EDITOR:

In the article "Timolol-pilocarpine combined vs timolol and pilocarpine given separately," by M. B. Söderström, Ö. Wallin, P.-A. Granström, and W. Thornburn (Am. J. Ophthalmol. 107:465, May 1989), the authors state that the patients included in the study had intraocular pressures greater than 21 mm Hg after one week of timolol use. The baseline pressures before treatment with timolol, however, were not stated. The timolol effect appeared to be minimal, because the mean pressures on day 0 were high (27 to 28 mm Hg). If an additive effect is to be shown that warrants combined therapy, the timolol must be proven to be contributing to the hypotensive effect.

Without information concerning the effect of timolol alone, this study may be documenting the effect of pilocarpine 4% given three times daily as compared with twice daily. We are sure this information would contribute to the value of the study.

ORNA GEYER, M.D.
LEONARD ROTHKOFF, M.D.
MOSHE LAZAR, M.D.
Tel Aviv, Israel

Reply

EDITOR:

The purpose of our study was to compare the effect on intraocular pressure of a solution containing timolol and pilocarpine with that of the two drugs given separately in patients not adequately controlled on a regimen of timolol alone. There was statistically significant additional pressure reduction in both treatment groups.

Patients who fulfilled the admission criteria entered a one- to three-week baseline period (three weeks for previously untreated patients) and received a study bottle of timolol. We gave patients previously treated with timolol a baseline run-in because of the clinical impression that patients participating in clinical studies tend to be more compliant with their treatment. Several patients also failed to meet the inclusion criterion of an intraocular pressure greater than 21 mm Hg after the baseline period. Among the 80 patients included were 19 in whom diagnosis was recent and previously untreated. In this group, the prestudy mean intraocular pressure was 38 mm Hg. One reason for the high intraocular pressure was the predominance of patients with capsular glaucoma. After the baseline period with timolol therapy, the mean intraocular pressure was reduced to 29 mm Hg.

The remaining 61 patients had been treated with timolol previously for varying periods of time. We do not believe that this group of patients responded differently to their timolol treatment because resistance to this drug is extremely rare. The additional pressure reduction caused by the pilocarpine is an additive effect.

MATS B. SÖDERSTRÖM, M.D.
PER-ARNE GRANSTRÖM, M.D.
Huddinge, Sweden
ÖRJAN WALLIN, M.D.
Stockholm, Sweden
WILLIAM THORBURN, M.D.
Hudiksvall, Sweden

BOOK REVIEWS

Edited by H. Stanley Thompson, M.D.

Intraocular Lenses. Evolution, Designs, Complications, and Pathology. By David J. Apple, Nick Mamalis, Randall J. Olson, and Marilyn C. Kincaid. Baltimore, Williams & Wilkins, 1989. 533 pages, index, illustrated. $199.95

Reviewed by Hans E. Grossniklaus
Atlanta, Georgia

An estimated 1 million intraocular lenses are implanted annually in the United States, which suggests that the effects of intraocular lenses on tissue are an important topic. In their first five years of work (1983–1988), investigators at the Center for Intraocular Lens Research examined 3,462 specimens, consisting primarily of explanted intraocular lenses and globes with intraocular lenses. This text is based on the study of these specimens, and it is the most comprehensive work to date on the subject of intraocular lenses.

Virtually everything an ophthalmologist would want to know about intraocular lenses is included. The text is divided into four sections: the evolution of intraocular lenses, designs and methods of fixation, pathology of intraocular lenses, and intraocular lens manufacture. Each section contains two to eight chapters. The first section chronicles the history of intraocular lenses and the people involved in their development. The second section describes in some detail the designs and the characteristic complications of iris-supported, anterior chamber, and posterior chamber intraocular lenses. A special chapter illustrating new concepts in intraocular lens design and implantation (including disk lenses, injectable lenses, and foldable lenses) is included in this section. The third section covers pathologic changes in eyes with intraocular lenses. It includes chapters specifically devoted to corneal, retinal, and iris complications. An exceptionally thorough discussion of the effects of the YAG laser on intraocular lenses is tucked away at the end of Chapter 12. The final section includes chapters on the biocompatibility of lens implant materials in the eye and various manufacturing defects of intraocular lenses.

The book is bountifully illustrated with high quality photographs including clinical and gross examination photographs, photomicrographs, and transmission and scanning electron micrographs. The 1,700 references are cited throughout the text. A separate appendix lists all the publications of the Center for Intraocular Lens Research. The index is thorough. Although the reader must often skip around from page to page or chapter to chapter to find photographs corresponding with text, and there are a few mistakes in figure citations in the text, these are minor flaws.

Recurrent themes include ophthalmology's indebtedness to intraocular lens pioneers (especially Dr. Harold Ridley), the importance of minimizing contact of intraocular lenses with uveal tissue, and the paramount value of a smooth, high quality surface on intraocular lenses. Of special note is the unique intraocular lens design pictured in the final two illustrations in the book; a design that must be dear to the senior author's heart.

This book marks a milestone in the study of intraocular lenses; every lens implant surgeon should read it, as should anyone with an interest in intraocular lenses.

Clinical Anatomy of the Eye. By Richard Snell and Michael A. Lemp. Cambridge, Massachusetts, Blackwell Scientific Publications, 1989. 364 pages, index, illustrated. $94.95

Reviewed by Gerhard W. Cibis
Kansas City, Missouri

Two experts in the teaching of anatomy and ophthalmology have combined their talents to provide clinicians with a new text-atlas of the anatomy of the eye. Clinical points are made throughout the text and in a clinical problems question and answer section at the end of each chapter. Here cases are used that illustrate the anatomic material covered. Working through

these cases highlights the clinical significance of structures and relationships.

Chapters are divided not only by structure but also by function. Highlighted paragraph headings introduce associated structures and related clinical functions. Blue section titles in the margins group these together in outline form. This format greatly aids the clinician seeking an anatomic answer to a specific clinical question and guides the beginner toward an appreciation of structural and clinical interrelationships.

Care has been taken with the design of the book. The typefaces used and the page layouts are pleasing. Most of the illustrations are new and are designed to make a clinical point. The line drawings are often color enhanced, for example, red for arteries and blue for veins. Ten plates of full-color paintings combine all structures in the classic anatomy atlas fashion.

There are 12 chapters: Embryology; Anatomy of the skull; Orbital cavity; Paranasal sinuses; Ocular appendages; Eyeball; Anatomy of the eyeball as seen with the ophthalmoscope, slit lamp, and gonioscope; Movements of the eyeball and the extraocular muscles; Orbital blood vessels; Orbital nerves; Autonomic nervous system; and Visual pathway.

The most stunning aspect of this book is that the authors serve the needs of all levels of expertise. The experienced clinician will refer to it for specific anatomic clinical points while deriving pleasure in the insightful ways they are described and illustrated.

Books Received

Ophthalmology. A Diagnostic Text. By William H. Coles. Baltimore, Williams & Wilkins, 1989. Softcover, 402 pages, index, illustrated. $29.95

This book is for medical students and residents. The first two thirds is a standard ophthalmic text for students and the final third is in a dictionary format, an annotated alphabetical listing of words, phrases, techniques, topics, and definitions.

Ophthalmology. What Shall I Do? By Jack J. Kanski and Bev Daily. Stoneham, Massachusetts, Butterworths, 1989. 71 pages, index, illustrated. $17.95

This slim book is written in a comfortable style for the general practitioner who would like to know a little more about eye problems, especially the ones that should be urgently referred to an ophthalmologist. No one on the western shores of the Atlantic will know what is meant by ". . . evert the upper eyelid with a Swan Vesta," but the reader should not find it difficult to dodge these English peculiarities.

The Book List

Anesthetic Surgery of the Eyelids. By Raul Loeb. New York, Springer-Verlag, 1989. 155 pages, index, illustrated. $175

Decade of Decision. The American Academy of Ophthalmology 1979–1989. By William Campbell Felch. San Francisco, Foundation of the American Academy of Ophthalmology, 1989. Softcover, 175 pages, index, illustrated.

Guide to Clinical Preventive Services. An Assessment of the Effectiveness of 169 Interventions. Report of the U. S. Preventive Services Task Force. Edited by Michael Fisher. Baltimore, Williams & Wilkins, 1989. Softcover, 419 pages, index. $19.95

Inherited and Environmentally Induced Retinal Degenerations. Edited by Matthew M. LaVail, Robert E. Anderson, and Joe G. Hollyfield. New York, Alan R. Liss, Inc., 1989. 727 pages, index, illustrated. $150

Introduction to Ophthalmology, ed. 5. By John Parr. Oxford, Oxford University Press, 1989. Softcover, 233 pages, index, illustrated. $35

Myopia Surgery. Anterior and Posterior Segments. Edited by Frank B. Thompson. New York, Macmillan Publishing Co., Inc., 1990. 338 pages, index, illustrated. $95

Oculoplastic and Orbital Emergencies. Edited by John V. Linberg. Norwalk, Connecticut, Appleton & Lange, 1990. 237 pages, index, illustrated. $39.95

Pneumatic Retinopexy. A Clinical Symposium. Edited by Paul E. Tornambe and W. Sanderson Grizzard. Chicago, Greenwood Publishing, 1989. 253 pages, index, illustrated. $69.95

The Visual Fields. Text and Atlas of Clinical Perimetry, ed. 6. By David O. Harrington and Michael V. Drake. St. Louis, C. V. Mosby, 1990. 405 pages, index, illustrated. $53.95

ABSTRACT DEPARTMENT

Edited by David Shoch, M.D.

Acta Ophthalmologica

Uncomplicated retrobulbar neuritis and the development of multiple sclerosis. Anmarkrud, N., and Slettnes, O. N. (Eye Dept., Lillehammer Fylkessykehus, N-2600 Lillehammer, Norway). Acta Ophthalmol. 67:306, 1989.

A retrospective study of 30 patients hospitalized with a diagnosis of uncomplicated retrobulbar neuritis was carried out. The follow-up period was 2-11 years; 57% developed multiple sclerosis. When the initial examination revealed oligoclonal bands in the cerebrospinal fluid, the risk of developing multiple sclerosis increased to 79%. With normal cerebrospinal fluid the risk decreased to only 10%. In the majority of cases, the diagnosis of multiple sclerosis was made during the first three years after retrobulbar neuritis. (1 figure, 4 tables, 18 references)—Authors' abstract

American Journal of Human Genetics

Linkage analysis of families with hereditary retinoblastoma: nonpenetrance of mutation, revealed by combined use of markers within and flanking the RBI gene. Scheffer, H., te Meerman, G. J., Kruize, Y. C., van den Berg, A. , Penninga, D. F., Tan, K., der Kinderen, D. J., and Buys, C. (Dept. Human Genet., State Univ. Groningen, Antonius Deusinglaan 4, NL-9713 AW Groningen, The Netherlands). Am. J. Hum. Genet. 45:252, 1989.

Approximately 40% of retinoblastomas are hereditary. About 10% are caused by transmission of the germ line mutation from the affected parent and 30% are caused by a new germ cell mutation. The inheritance pattern is dominant with a penetrance of about 90%. Retinoblastoma is caused by two mutational events: in the inherited form the first mutation is in the germ cell and is present in all somatic cells, the second mutation occurs in the somatic cell. In the nonhereditary form both mutations occur in the same somatic cell. In some hereditary tumors there is deletion of band 13q14. Some mutation carriers are never affected although the retinal cells have a retinoblastoma locus in one of the alleles. Apparently the second mutation involving the normal allele does not occur.

The authors developed a method to determine the fraction of unaffected offspring who carry a predisposing mutation. The technique requires the use of DNA markers both within and flanking the retinoblastoma gene. In 19 families with hereditary retinoblastoma the carrier was identified in two families and showed nonpenetrance of the mutation predisposing to retinoblastoma. Intragenic markers were informative in 15 pedigrees. When flanking markers from the same chromosomal region were used there was an increase in the number of informative families to 18. Thus, there is a high probability of carrier detection in families with hereditary retinoblastoma if both intragenic and flanking markers are used. (4 figures, 2 tables, 33 references)—David Shoch

Annals of Neurology

Abnormal pattern electroretinogram in Alzheimer's disease: evidence for retinal ganglion cell degeneration? Katz, B., Rimmer, S., Iragui, V., and Katzman, R. (Pacific Presbyterian Med. Ctr., Smith-Ketterwell Eye Res. Inst., 2340 Clay St., San Francisco, CA 94115). Ann. Neurol. 26:221, 1989.

The loss of visual function in Alzheimer's disease is well documented and has been assumed to be the result of changes in the cerebral cortex. More recently there has been some evidence that changes may also take place in the retina. To test this hypothesis the authors studied pattern reversal electroretinograms, flash electroretinograms, pattern reversal visual-evoked potentials and flash visual-evoked potentials in six patients with Alzheimer's disease and in six age- and sex-matched control subjects. The flash electroretinogram is commonly thought to be generated in the photoreceptors, Müller cells, and the retinal pigment epithelium. The pattern reversal electroretinogram is thought to be generated by the ganglion cell axons. The mean amplitude of the pattern reversal electroretinogram was significantly less

in the Alzheimer's patients than in the control group (P = .004). This is interpreted as degeneration of retinal ganglion cells and axonal depletion within the optic nerve. The patients had normal pattern reversal visual-evoked potentials and flash electroretinograms. (2 figures, 3 tables, 38 references)—David Shoch

Abnormal pattern electroretinograms in patients with senile dementia of the Alzheimer type. Trick, G. L., Barris, M. C., and Bickler-Bluth, M. (Dept. Ophthalmol., Box 8096, Washington Univ. School of Med., 660 S. Euclid Ave., St. Louis, MO 63110). Ann. Neurol. 26:226, 1989.

Evidence suggests that there are degenerative changes in both the primary visual pathway and the visual association areas in patients with Alzheimer's disease. In addition to cortical changes there may be changes in retinal ganglion cell function which contribute to the visual loss in these patients. A group of 13 patients with Alzheimer's disease were tested by pattern reversal electroretinography using both low and high rates of reversal. There were 30 age-matched control subjects. Patients with Alzheimer's disease had significant amplitude reductions as compared to the controls. This amplitude reduction was most pronounced with a high temporal frequency condition. These results support the hypothesis that retinal ganglion cell dysfunction occurs in Alzheimer's disease and that it affects the larger, faster-conducting retinal ganglion cells together with their retinocortical projections. (4 figures, 38 references)—David Shoch

Archives of the Diseases of Childhood

Night blindness and conjunctival xerosis caused by vitamin A deficiency in patients with cystic fibrosis. Rayner, R. J., Tyrrell, J. C., Hiller, E. J., Marenah, C., Neugebauer, M. A., Vernon, S. A., and Brimlow, G. (City Hosp., Hucknall Rd., Nottingham NG5 1PB). Arch. Dis. Child. 64:1151, 1989.

The two major ocular signs of vitamin A deficiency are night blindness, caused by a defect in the synthesis of rhodopsin, and a keratinizing squamous metaplasia of the conjunctiva. In 43 patients with cystic fibrosis, who were aged 8 to 44 years, eight were found to have abnormal dark adaptation and three had conjunctival xerosis. Five of the patients were treated with 100,000 to 200,000 IU of vitamin A orally. In four of these patients dark adaptation tests were repeated and three were normal. One patient required three additional doses of water soluble vitamin A and a daily supplement of 12,000 units of vitamin A before the dark adaptation threshold was normal. The authors believe that adolescents with cystic fibrosis are at risk to develop night blindness and conjunctival xerosis and must be given daily vitamin supplements. (3 figures, 2 tables, 20 references)—David Shoch

Archives of Neurology

Neurologic eye signs following motorcycle accidents. Keane, J. R. (Reprints not available). Arch. Neurol. 46:761, 1989.

The incidence of neuro-ophthalmologic injuries following motorcycle accidents is similar to that caused by other forms of closed head trauma except that there is a higher incidence of trochlear nerve palsy. The death rate per mile is six times higher for motorcycle accidents than automobile accidents. In 1976 repeal or weakening of compulsory helmet laws in 26 states was followed by a 44% increase in motorcycle fatalities between 1976 and 1979.

The cost per injured motorcyclist in one major trauma center averaged about $26,000, 64% of which was paid by public funds. (1 table, 13 references)—David Shoch

British Journal of Radiology

The use of real-time orbital ultrasound in Graves' ophthalmopathy: a comparison with computed tomography. Given-Wilson, R., Pope, R. M., Michell, M. J., Cannon, R., and McGregor, A. M. (Depts. Radiol. & Med., King's College Hosp., Denmark Hill, London SE5 8RX). Br. J. Radiol. 62:705, 1989.

The diagnosis of Graves' ophthalmopathy is sometimes difficult to establish because the patient may be euthyroid and currently there are no reliable immunologic markers of disease activity. Computed tomography is valuable but there is hesitation about routine, repeated use because of radiation to the lens. The authors standardized ultrasound scanning to measure the diameter of the medial rectus muscle. They compared this measurement in 20 patients with proven Graves' ophthalmopathy and 21 normal subjects. The normal values ranged from 1.75 mm to 4.07 mm. There were significantly larger values observed in patients with Graves' disease with a good correlation between the medial rectus muscle diameter and the clinical index of severity ($P < .001$). There was a good correlation between the enlargement measured by scanning and the measurement made with computed tomography. The upper limit of normal for diameter of the medial rectus muscle appears to be 4.07 mm. Orbital ultrasound is cheaper, and has less risk than computed tomography. The authors reserve computed tomography for patients with ophthalmoplegia and a normal sized medial rectus muscle since such patients may have involvement of the inferior rectus muscle only. (4 figures, 1 table, 16 references)—David Shoch

British Medical Journal

"Operation cataract": a means of reducing waiting lists for cataract operations. Thomas, H. P., Darvell, R. H., and Hicks, C. (Princess Margaret Hosp., Swindon, Wiltshire, England). Br. Med. J. 299:961, 1989.

In 1986, 58,000 people in England and Wales were on ophthalmic waiting lists, most awaiting cataract surgery. Seventeen percent of the patients had been waiting for over a year. Two years later the waiting list had increased to 66,000 people. It was estimated that given the volume of surgery at that time in England and Wales it would take six months to clear the backlog.

In the district in which the authors work there were 217 patients on a waiting list for cataract surgery. In order to reduce the number of patients the authors carried out "operation cataract" over ten days in November 1988. One hundred patients were chosen from the waiting list by excluding those who had moved elsewhere, had died, or were judged to be unsuitable for surgery because of poorly controlled diabetes or dementia.

Patients were brought in from outlying areas by bus and housed in a local hotel. Sixteen or 17 cataract operations were done per day over six days. Five ophthalmologists performed the operations. There were extra costs involved for overtime payments but the authors estimate that the unit cost was about £600 per operation. The waiting list for cataract operations was halved. Thirty-seven patients had been waiting more than one year for their cataract removal. (2 figures, 4 references)—David Shoch

Diabetologica

Effect of antihypertensive treatment on blood-retinal barrier permeability to fluorescein in hypertensive Type 1 (insulin-dependent) diabetic patients with background retinopathy. Parving, H. H., Larsen, M., and Lund-Andersen, H. (Hvidore Hospital, Emiliekildevej 1, DK-2930 Klampenborg, Denmark). Diabetologica 32:440, 1989.

Nine patients with diabetes mellitus and background retinopathy had fundus photography, fluorescein angiography, and vitreous fluorometry performed before and after the institution of antihypertensive therapy. The average interval between the two examinations was seven months with extremes of three to 13 months. The standard treatment was the administration of captopril and a diuretic. There was a significant lowering in the vascular hypertension ($P < .05$) and the blood-retinal barrier leakage of fluorescein decreased from 2.4 ± 1.1 to $1.4 \pm 0.5 \times 10\ -7$ cm/sec.

The study suggests that increased systemic blood pressure contributes to an abnormal blood-retinal barrier permeability and that diabetics with background retinopathy should be treated for their systemic hypertension since the blood-retinal permeability can be reduced by reducing systemic blood pressure. (2 tables, 33 references)—David Shoch

Neurology

Ocular pseudomyasthenia or ocular myasthenia 'plus.' Moorthy, G., Behrens, M. M., Drachman, D. B., Kirkham, T. H., Knox, D. L., Miller, N. R., Slamovitz, T. L., and Zinreich, S. J. (The Johns Hopkins Hosp., Baltimore, MD 21205). Neurology 39:1150, 1989.

Eight patients with classic myasthenia gravis with blepharoptosis responded to treatment with anticholinesterase medication. In all patients there was a gradual progression of symptoms and eventually intracranial lesions were found instead of, or in addition to, the myasthenia gravis. These lesions included parasellar tumors and aneurysms. It is essential in patients having the signs of myasthenia gravis to establish the diagnosis definitively. The authors advise evaluating all such patients for intracranial mass lesions using computed tomography or magnetic resonance imaging. They believe the presence of serum antibodies to acetycholine receptor is virtually diagnostic of myasthenia gravis. (3 figures, 21 references)—David Shoch

Oculomotor palsy with cyclic spasms. Friedman, D. I., Wright, K. W., and Sadun, A. A. (Dept. Ophthalmol. Univ. Southern California, 1355 San Pablo St., Los Angeles, CA 90033). Neurology 39:1263, 1989.

The only significant finding in a 3-year-old healthy boy was a left pupil that varied in size from 3 to 7 mm over a period of 90 seconds. As the pupil enlarged the left eyelid drooped, producing a 2 to 3-mm blepharoptosis. When the pupil constricted the eyelid then again elevated. The right eyelid and pupil were entirely normal. The child was orthophoric but there was a moderate restriction of supraduction and infraduction of the left eye.

These cycles persist during sleep and are present for the lifetime of the patient. The cause in not known but since it is unilateral, it is probably caused by a peripheral oculomotor lesion. An aberrant nerve regeneration has been suggested as a cause. The process worsened when the body temperature was increased and complete eye closure occurred when the body temperature rose above 103 F, which suggests a demyelinating lesion probably in the subarachnoid space. (1 figure, 5 references)—David Shoch

New England Journal of Medicine

The relative risk of ulcerative keratitis among users of daily-wear and extended-wear soft contact lenses. Schein, O. D., Glynn, R. J., Poggio, E. C., Seddon, J. M., Kenyon, K. R., and Microbial Keratitis Study Group. (243 Charles St., Boston, MA 02114) N. Engl. J. Med. 321:773, 1989.

This multicenter study is based on 86 patients with ulcerative keratitis. The control group consisted of 61 patients who reported with problems unrelated to contact lenses and 410 population based controls found by telephone survey using random digit dialing.

The relative risk of ulcerative keratitis for patients wearing extended-wear lenses as compared to daily-wear lenses was 3.90. Among the hospital based controls the risk was 4.21. When the extended-wear lens wearers divided into those who only wore lenses during the day and those who wore lenses overnight, the users of extended-wear lenses had a risk ten to 15 times greater than the daily-wear lens wearers who did not wear lenses overnight. Thus, the risk of ulcerative keratitis was incrementally related to the extent of overnight wear. (4 tables, 16 references)—David Shoch

The incidence of ulcerative keratitis among users of daily-wear and extended-wear soft contact lenses. Poggio, E. C., Glynn, R. J., Schein, O. D., Seddon, J. M., Shannon, M. J., Scardino, V. A., and Kenyon, K. R. (55 Wheeler St., Cambridge, MA 02138). N. Engl. J. Med. 321:779, 1989.

A mail interview of 641 ophthalmologists in the New England area disclosed 195 cases of ulcerative keratitis. A telephone survey was conducted by random digit dialing to estimate the incidence of contact lens wear. The authors calculated an annual incidence of ulcerative keratitis of 20.9/10,000 persons for extended-wear soft contact lens wearers. Among daily-wear soft contact lens wearers the annual incidence was 4.1/10,000 persons. (4 tables, 19 references)—David Shoch

NEWS ITEMS

Send News Items to
American Journal of Ophthalmology
435 N. Michigan Ave., Suite 1415
Chicago, IL 60611

The Journal invites readers to submit announcements concerning meetings, postgraduate courses, lectures, honors, and appointments. Each item must be typed double-spaced on bond paper with 1½-inch margins. Only one news item should be submitted on each page. Announcements concerning meetings and courses must contain the title, location, dates, sponsors, and address required for additional information. Each item must not exceed 75 words in length and be prepared in narrative, not outline, form. Announcements of meetings and courses must be received at least four months before the event.

Tenth Annual Alamo City Ophthalmology Clinical Conference

The Tenth Annual Alamo City Ophthalmology Clinical Conference, sponsored by the Department of Ophthalmology of the University of Texas Health Science Center, Brooke Army Medical Center, and Wilford Hall, will be held March 2 and 3, 1990, in San Antonio, Texas. For further information, write Johan T. Zwaan, M.D., Department of Ophthalmology, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Dr., San Antonio, TX 78284.

Foundation for Glaucoma Research: Glaucoma—Management into the 21st Century

The Foundation for Glaucoma Research: Glaucoma—Management into the 21st Century Course will be held May 18 and 19, 1990, in San Francisco. For further information, write Course Coordinator, Foundation for Glaucoma Research, 490 Post St., Suite 830, San Francisco, CA 94102; telephone (415) 986-3162.

Howard University: Ocular Phototoxicity Symposium

The Howard University: Ocular Phototoxicity Symposium will be held March 9 and 10, 1990, in St. Thomas, U. S. Virgin Islands. For further information, write Claude L. Cowan, Jr., M.D., Howard University Hospital Division of Ophthalmology, 2041 Georgia Ave., N.W., Washington, DC 20060; telephone (202) 865-1257.

Humana Hospital—Lexington: Clinical Advances in Treatment of Retina, Vitreous and Uveal Diseases for the Practicing Ophthalmologist

The Humana Hospital—Lexington: Clinical Advances in Treatment of Retina, Vitreous and Uveal Diseases for the Practicing Ophthalmologist Course will be held April 6 and 7, 1990, at Marriott's Griffin Gate Resort, Lexington, Kentucky. For further information, write Karen Heidorn, Humana Hospital-Lexington, 150 N. Eagle Creek Dr., Lexington, KY 40509; telephone (606) 268-3754.

Manhattan Eye, Ear and Throat Hospital: Vitrectomy in Anterior and Posterior Segment Surgery

The Manhattan Eye, Ear and Throat Hospital: Vitrectomy in Anterior and Posterior Segment Surgery Course will be held April 21, 1990, in New York City. For further information, write Francine Leinhardt, Course Coordinator, Manhattan Eye, Ear and Throat Hospital, 210 E. 64th St., New York, NY 10021; telephone (212) 838-9200, ext. 2776.

Pacific Coast Oto-Ophthalmological Society: 74th Annual Meeting

The Pacific Coast Oto-Ophthalmological Society: 74th Annual Meeting will be held June 19–23, 1990, at the Four Seasons Hotel, Vancouver, British Columbia. For further information, write Mireya Jones, PCOOS Manager, 1613 Chelsea Rd., Suite 229; San Marino, CA 91108; telephone (818) 799-8610.

Rochester Ophthalmologic Society and University of Rochester School of Medicine and Dentistry: Annual Ophthalmology Conference and 35th Annual Albert C. Snell Memorial Lecture

The Rochester Ophthalmologic Society and University of Rochester School of Medicine and Dentistry: Annual Ophthalmology Conference featuring the 35th Annual Albert C. Snell Memorial Lecture will be held April 6 and 7, 1990, at the Rochester Academy of Medicine, Rochester, New York. For further information, write University of Rochester Medical Center, Office of Continuing Professional Education, 601 Elmwood Ave., Box 677, Rochester, NY 14642; telephone (716) 275-4392.

Basic Science Course in Ophthalmology at Stanford

The Basic Science Course in Ophthalmology at Stanford, sponsored by the Department of Ophthalmology, Stanford University Medical Center in cooperation with the University of California, Davis; Pacific Presbyterian Medical Center; and the University of California, San Francisco, will be held July 2–Aug. 31, 1990. For further information, write Basic Science Course, P. R. Egbert, M.D., Director, Department of Ophthalmology, A-157, Stanford Medical Center, Stanford, CA 94305.

Wills Eye Hospital: 15th Annual Ophthalmology Review Course

The Wills Eye Hospital: 15th Annual Ophthalmology Review Course will be held March 24–28, 1990, at the Sheraton Society Hill Hotel, Philadelphia. For further information, write Wills Eye Hospital, Department of Continuing Medical Education, Ms. Lucia M. Manes, 9th and Walnut Streets, Philadelphia, PA 19107; telephone (215) 928-3378.

National Society to Prevent Blindness: 1990 Burroughs Wellcome Research Fellowship in Ophthalmology

The National Society to Prevent Blindness: 1990 Burroughs Wellcome Research Fellowship in Ophthalmology is intended to provide basic science research training in ophthalmology for a physician who has completed a residency in ophthalmology. The fellowship has an annual stipend of $25,000 and $2,000 for laboratory expenses and travel incidental to fellowship training; a second-year extension is optional. For further information, write Pamela Peters, National Society to Prevent Blindness, 500 E. Remington Rd., Schaumburg, IL 60173; telephone (708) 843-2020.

American Academy of Ophthalmology: New Officers

George E. Garcia, Boston, is president of the American Academy of Ophthalmology; George W. Weinstein, Morgantown, West Virginia, is president-elect; Thomas Fry, Falls Church, Virginia, and Edward K. Isbey, Ashville, North Carolina, are directors at large; H. Dunbar Hoskins, San Franscisco, is secretary for the annual meeting; Richard P. Mell, Seattle, is secretary for public and professional information; and Hunter R. Stokes, Florence, South Carolina, secretary for representation.

San Diego County Ophthalmological Society: New Officers

The San Diego County Ophthalmological Society: New Officers for 1989-1990 are as follows: Geves Kenny, president; Robert N. Weinreb, vice president; Paul Tornambe, secretary; and John Bokosky, treasurer.

Personal

Richard L. Anderson

Richard L. Anderson, professor of ophthalmology and director of oculoplastic, orbital, and oncologic surgery at the University of Utah, received the annual award of the Society of Heed Fellows in New Orleans. Dr. Anderson was a Heed Fellow at the Albany Medical Center with Orkan Stasior and at the University of California Medical Center with Crowell Beard.

VOLUME 109

FEBRUARY 15

1990

14.12.90

AMERICAN JOURNAL OF OPHTHALMOLOGY

Monthly since 1884

• ORIGINAL ARTICLES

Intraconazole for *Acanthamoeba* Keratitis
Ishibashi, Matsumoto, Kabata, Watanabe, Hommura, Yasuraoka, Ishii

Eikenella corrodens
Klein, Couch, Thompson

Cyclosporine-Containing Collagen Shields
Chen, Gebhardt, Reidy, Kaufman

Chronic Conjunctivitis
Rapoza, Quinn, Terry, Gottsch, Kiessling, Taylor

Penetrating Keratoplasty in Down's Syndrome
Frantz, Insler, Hagenah, McDonald, Kaufman

Retinal Detachment in Penetrating Keratoplasty
Sternberg, Meredith, Stewart, Kaplan

Hemorheology and AIDS
Engstrom, Holland, Hardy, Meiselman

Corneal Topography After Epikeratophakia for Aphakia
Maguire

Trabeculectomy for Inflammatory Glaucoma
Jampel, Jabs, Quigley

Contact Lens for Transscleral Nd:YAG Cyclophotocoagulation
Simmons, Blasini, Shields, Erickson

Extracellular Matrix in Glaucomatous Optic Disk
Hernandez, Andrzejewska, Neufeld

Adrenergic Effects on Outflow Facility in the Cynomolgus Monkey
Robinson, Kaufman

Traumatic Esotropia
Pollard

Myopia Induced by Vitreous Hemorrhage
Miller-Meeks, Bennett, Keech, Blodi

Birdshot Retinochoroidopathy
Soubrane, Bokobza, Coscas

Choroid and Age-Related Bruch's Membrane Change
Pauleikhoff, Chen, Chisholm, Bird

Microinstrumentation for Vitreous Surgery
de Juan, Hickingbotham

• EDITORIAL

Peer Review
Newell

• LETTERS TO THE JOURNAL

Subretinal neovascularization
Leonardy, Dabbs, Sternberg

Chorioretinitis
Hirakata, Oshima, Azuma

Fibrin glue in orbital surgery
Bartley, McCaffrey

Microphthalmos with cyst and Edwards' syndrome
Guterman, Abboud, Mets

Bone marrow transplant in mucopolysaccharidosis
Christiansen, Smith, Henslee-Downey

Necrotizing scleritis in conjunctival squamous cell carcinoma
Kim, Seiff, Howes, O'Donnell

Paralimbal scleromalacia perforans
Mader, Stulting, Crosswell

Horizontal sectoral field defect after ischemic infarction
Grossman, Galetta, Nichols, Grossman

Tonic pupils as a result of botulism
Friedman, Fortanasce, Sadun

Intermittent pupillary dilatation
Berreen, Vrabec, Penar

Cyclosporine-induced trichomegaly
Weaver, Bartley

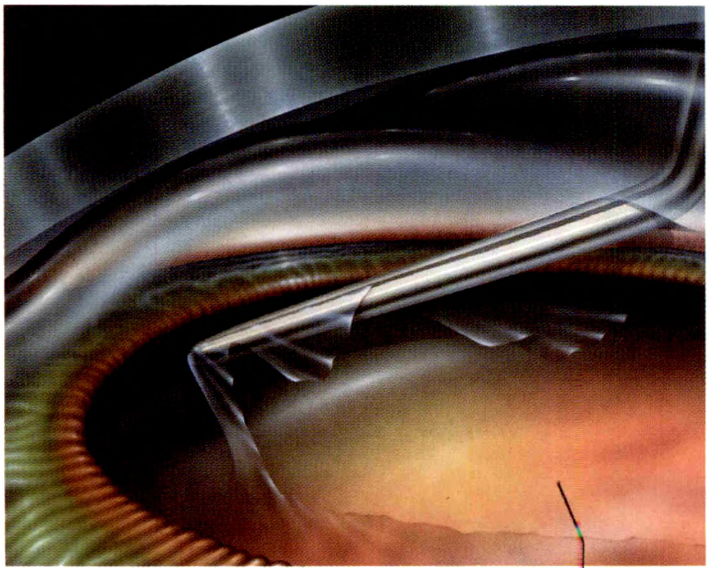
Acarine-infested eyelid
English, Zhang, McManus, Campbell

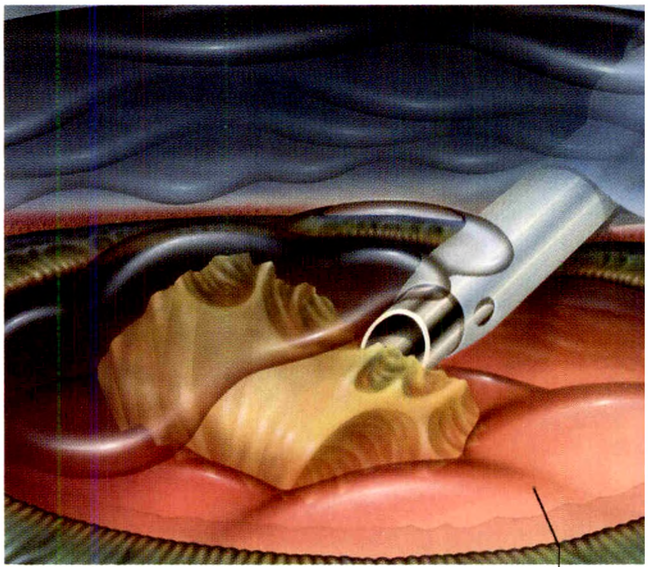
***Capnocytophaga canimorsus* causing corneal infection**
de Smet, Chan, Nussenblatt, Palestine

Microsporidia infection
Lowder, Meisler, McMahon, Longworth, Rutherford

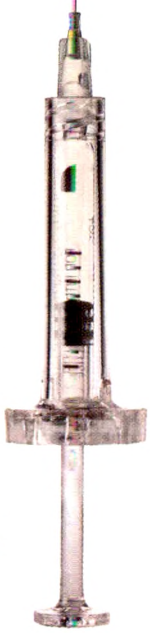
AJO®

It's like having a surgica





Facilitating capsulorhexis



"I use VISCOAT to make my tear capsulotomy easier and more consistent. As I use Utrata forceps to tear the anterior capsule, I want a well-maintained chamber for ease of movement as I grasp and regrasp the capsule. VISCOAT gives me that without the need for any additional irrigation. I find this beneficial, especially in cases with positive vitreous pressure where the tear is apt to run to the side."

C.J. Anderson, MD
Madison, Wisconsin

Preventing a capsular tear during phaco with VISCOAT®*

"It's important to be able to control the position of a jagged nuclear fragment with regard to the cornea and posterior capsule during phacoemulsification. By placing VISCOAT above and below the nucleus, I have this control and significantly reduce the risk of a capsular tear. With VISCOAT, I can slow down the movement of the nuclear fragments, thus gaining more time to control them. And the protective layer of VISCOAT remains on the capsule and the cornea throughout my phaco procedure."

Robert Schnipper, MD
Jacksonville, Florida

*U.S. Patent Pending

AJO® AMERICAN JOURNAL OF OPHTHALMOLOGY®

ISSN 0002-9394 February 1990 Series 3, Vol. 109, No. 2

GENERAL INFORMATION

Address typescripts to Frank W. Newell, M.D., Editor, AMERICAN JOURNAL OF OPHTHALMOLOGY, Suite 1415, 435 North Michigan Avenue, Chicago, IL 60611.

Manuscripts must be original material submitted solely to THE AMERICAN JOURNAL OF OPHTHALMOLOGY. Two copies must be submitted; the second copy may be machine-duplicated. The entire manuscript, including case reports, footnotes, and references, must be typed double-spaced, with 1½-inch margins, on 8½ by 11-inch heavy white bond paper. See Instructions to Authors published elsewhere in this issue. Copies of Instructions to Authors will be mailed on request. All manuscripts originating in the United States must be sent by first-class mail; those manuscripts originating outside the United States must be sent airmail. Receipt of manuscript is acknowledged immediately.

At the time of submission, a copyright transfer, published monthly in THE AMERICAN JOURNAL OF OPHTHALMOLOGY, signed by each of the authors must be included with the typescript. No article or letter will be reviewed until the signed copyright transfer is received.

Manuscripts submitted for consideration are reviewed by members of the Editorial Board and other experts in the field. An unpublished manuscript is a privileged document that must be protected from any form of exploitation. The reviewer should not cite the manuscript or refer to the work it describes before it has been published. Reviewers must refrain from using the information contained in the manuscript for the advancement of their own work, their colleagues' work, or their institution's work. Reviewers are consultants to the editor and are instructed not to discuss the paper with the authors. Reviewers work anonymously and their identity may not be revealed to authors or to others.

Edited typescripts sent to the author must be corrected and returned within 48 hours to Manuscript Editor, AMERICAN JOURNAL OF OPHTHALMOLOGY, Suite 1415, 435 North Michigan Avenue, Chicago, IL 60611.

Permission to reprint any portion of published articles must be obtained in writing from both the Ophthalmic Publishing Company and from the authors of the articles.

Reprints may be obtained from Ophthalmic Publishing Company, Suite 1415, 435 North Michigan Avenue, Chicago, IL 60611, if ordered at the time the typescript is returned.

Address news items and society proceedings to News Editor, AMERICAN JOURNAL OF OPHTHALMOLOGY, Suite 1415, 435 North Michigan Avenue, Chicago, IL 60611.

Exchange copies of medical journals should be sent to David Shoch, M.D., Suite 1415, 435 North Michigan Avenue, Chicago, IL 60611.

Subscriptions: Subscriptions, requests for single issues, notices of change of address, advertising and other communications should be sent to Ophthalmic Publishing Company, Suite 1415, 435 North Michigan Avenue, Chicago, IL 60611. Notices of change of address must be received at least 60 days in advance and must include both old and new addresses and AJO identification number.

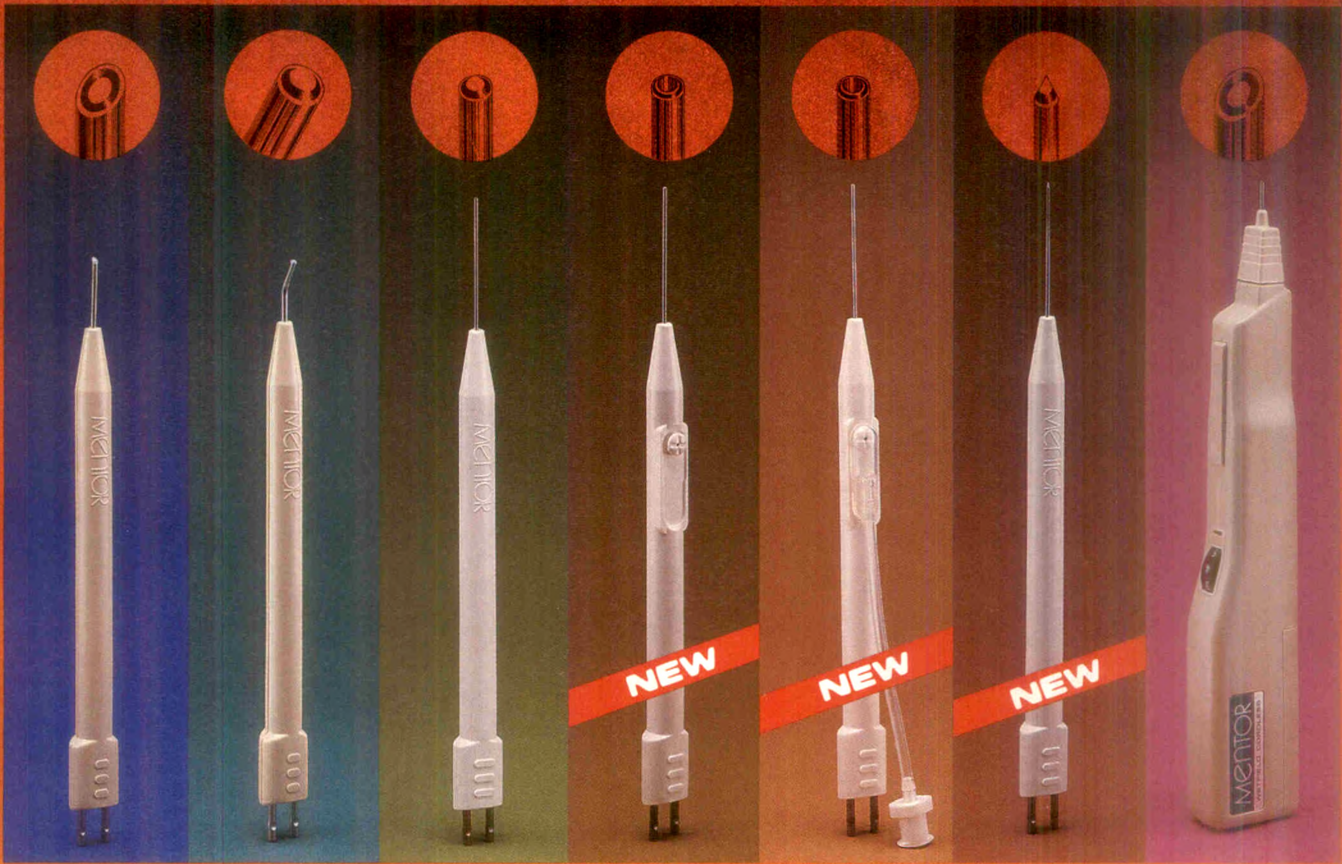
Send claims for issues not received no later than two months after the issue date for domestic and Canadian subscribers and four months after the issue date for all other foreign subscribers. Address claims to Circulation Coordinator, Ophthalmic Publishing Company, Suite 1415, 435 North Michigan Avenue, Chicago, IL 60611.

Advertising: Insertion orders, copy, and materials should be sent to the Media Planner and must be received by the 20th of the second preceding month that the advertisement is scheduled. Consult the Media Planner for extensions, rates, and media kits at THE AMERICAN JOURNAL OF OPHTHALMOLOGY, Suite 1415, 435 North Michigan Avenue, Chicago, IL 60611; telephone (312) 787-3853; FAX (312) 787-5186.

THE AMERICAN JOURNAL OF OPHTHALMOLOGY is published monthly by the Ophthalmic Publishing Company, Suite 1415, 435 North Michigan Avenue, Chicago, IL 60611. The subscription rates in the United States are as follows: one year, $48.00, two years, $90.00. In Canada and all other foreign countries, the rates are as follows: one year, $75.00; two years, $140.00; paid in U.S. bank draft or international money order. Single issues are available for $10.00 in the United States and for $13.00 in all other countries. Subscription and Advertising Office: Ophthalmic Publishing Company, Suite 1415, 435 North Michigan Avenue, Chicago, IL 60611.

 Second class postage paid at Chicago, Illinois, and at additional mailing offices. Printed in U.S.A. POSTMASTER: Send address changes to Ophthalmic Publishing Co., Suite 1415, 435 North Michigan Avenue, Chicago, IL 60611.

Dependable bipolar hemostasis from the pioneer in WET-FIELD® technology



1250: 18 gauge - efficiency and economy for scleral bleeders.

1251: 18 gauge - same advantages but with 45 degree curved shaft.

1260: 20 gauge - for controlling retinal bleeders.

1261: 20 gauge - retinal hemostasis plus passive aspiration.

1262: 20 gauge - retinal hemostasis plus active aspiration and reflux.

1265: 23 gauge tapered - retinotomies, deep anterior segment bleeders.

Cordless: 18 gauge - same precision but totally self contained.

Mentor® WET-FIELD Hemostatic Erasers™

Mentor Hemostatic Erasers continue to set new standards for pinpoint hemostasis in both the anterior and posterior segments.

Our years of manufacturing experience are your assurance that safety, reliability and consistency are built into each and every unit.

Two of our newest additions have innovative provisions for passive aspiration and active aspiration and reflux. The third is a 20 gauge tapered to 23 gauge and beveled to a fine point. Now surgeons have all the advantages of bipolar hemostatic control for intraocular procedures.

All Hemostatic Erasers are sold sterile and disposable for ultimate consistency and convenience. They are for use with Mentor WET-FIELD Coagulators including the new portable battery operated WET-FIELD II pictured at left.

For further information or to place an order, write or call toll free:
1-800-992-7557 (National); 1-617-871-6950 (Collect in MA)

MENTOR O&O INC.

3000 Longwater Drive, Norwell, MA 02061

Mentor WET-FIELD Hemostatic Erasers were developed in cooperation with Robert C. Drews, M.D., Clayton, Missouri.
Product 1261 was developed in cooperation with F.H. Davidorf, M.D., Columbus, Ohio.

Hemostatic Eraser is a trademark of Mentor O&O, Inc.

AJO® AMERICAN JOURNAL OF OPHTHALMOLOGY®

ISSN 0002-9394 February 1990 Series 3, Vol. 109, No. 2

TABLE OF CONTENTS

ORIGINAL ARTICLES

Oral itraconazole and topical miconazole with débridement for *Acanthamoeba* keratitis
Yasuhisa Ishibashi, Yujiro Matsumoto, Takamichi Kabata, Ryoko Watanabe, Sachiko Hommura, Kazuo Yasuraoka, and Keiich Ishii 121

Ocular infections associated with *Eikenella corrodens*
Betty Klein, Jeffrey Couch, and John Thompson 127

Cyclosporine-containing collagen shields suppress corneal allograft rejection
Y. F. Chen, B. M. Gebhardt, J. J. Reidy, and H. E. Kaufman 132

A systematic approach to the diagnosis and treatment of chronic conjunctivitis
Peter A. Rapoza, Thomas C. Quinn, Arlo C. Terry, John D. Gottsch, Lou Ann Kiessling, and Hugh R. Taylor 138

Penetrating keratoplasty for keratoconus in Down's syndrome
Jonathan M. Frantz, Michael S. Insler, Michael Hagenah, Marguerite B. McDonald, and Herbert E. Kaufman 143

Retinal detachment in penetrating keratoplasty patients
Paul Sternberg, Jr., Travis A. Meredith, Michael A. Stewart, and Henry J. Kaplan 148

Hemorheologic abnormalities in patients with human immunodeficiency virus infection and ophthalmic microvasculopathy
Robert E. Engstrom, Jr., Gary N. Holland, W. David Hardy, and Herbert J. Meiselman 153

Corneal topography of patients with excellent Snellen visual acuity after epikeratophakia for aphakia
Leo J. Maguire 162

Trabeculectomy with 5-fluorouracil for adult inflammatory glaucoma
Henry D. Jampel, Douglas A. Jabs, and Harry A. Quigley 168

Comparison of transscleral neodymium:YAG cyclophotocoagulation with and without a contact lens in human autopsy eyes
Ruthanne B. Simmons, Marino Blasini, M. Bruce Shields, and Phillip J. Erickson 174

Changes in the extracellular matrix of the human optic nerve head in primary open-angle glaucoma
M. Rosario Hernandez, Wieslawa M. Andrzejewska, and Arthur H. Neufeld 180

Effects and interactions of epinephrine, norepinephrine, timolol, and betaxolol on outflow facility in the cynomolgus monkey
James C. Robinson and Paul L. Kaufman 189

Accommodative esotropia after ocular and head injury
Zane F. Pollard 195

Myopia induced by vitreous hemorrhage
Mariannette J. Miller-Meeks, Stephen R. Bennett, Ronald V. Keech, and Christopher F. Blodi 199

Late developing lesions in birdshot retinochoroidopathy
Gisèle Soubrane, René Bokobza, and Gabriel Coscas 204

Choroidal perfusion abnormality with age-related Bruch's membrane change
D. Pauleikhoff, J. C. Chen, I. H. Chisholm, and A. C. Bird 211

Refinements in microinstrumentation for vitreous surgery
Eugene de Juan, Jr., and Dyson Hickingbotham 218

EDITORIAL

Peer review
Frank W. Newell 221

LETTERS TO THE JOURNAL

Subretinal neovascularization after operating microscope burn. *Nicholas J. Leonardy, Charles K. Dabbs, and Paul Sternberg, Jr.,* **224. Chorioretinitis induced by coxsackievirus B4 infection.** *Kyoko Hirakata, Takashi Oshima, and Noriyuki Azuma,* **225. Cryoprecipitated fibrinogen (fibrin glue) in orbital surgery.** *George B. Bartley and Thomas V. McCaffrey,* **227. Microphthalmos with cyst and Edwards' syndrome.** *Carl Guterman, Emad Abboud, and Marilyn B. Mets,* **228. Normal intraocular pressure after a bone marrow transplant in glaucoma associated with mucopolysaccharidosis type I-H.** *Stephen P. Christiansen, Thomas J. Smith, and P. Jean Henslee-Downey,* **230. Necrotizing scleritis secondary to conjunctival squamous cell carcinoma in acquired immunodeficiency syndrome.** *Robert Y. Kim, Stuart R. Seiff, Edward L. Howes, Jr., and James J. O'Donnell,* **231. Bilateral paralimbal scleromalacia perforans.** *Thomas H. Mader, R. Doyle Stulting, and Hal H. Crosswell, Jr.,* **233. Horizontal homonymous sectoral field defect after ischemic infarction of the occipital cortex.** *Murray Grossman, Steven L. Galetta, Charles W. Nichols, and Robert I. Grossman,* **234. Tonic pupils as a result of botulism.** *Deborah I. Friedman, Vincent N. Fortanasce, and Alfredo A. Sadun,* **236. Intermittent pupillary dilatation associated with astrocytoma.** *John P. Berreen, Michael P. Vrabec, and Paul L. Penar,* **237. Cyclosporine-induced trichomegaly.** *Daniel T. Weaver and George B. Bartley,* **239. Electron microscopic evidence of acarine infestation of the eyelid margin.** *Frank P. English, Guang Wen Zhang, Don P. McManus, and Phillip Campbell,* **239. *Capnocyto-***

(Table of Contents continued on Advertising Page 8)

AJO® AMERICAN JOURNAL OF OPHTHALMOLOGY®

ISSN 0002-9394 | February 1990 | Series 3, Vol. 109, No. 2

TABLE OF CONTENTS *(continued from Advertising page 6)*

***phaga canimorsus* as the cause of a chronic corneal infection.** *Marc D. de Smet, Chi Chao Chan, Robert B. Nussenblatt, and Alan G. Palestine,* **240. Microsporidia infection of the cornea in a man seropositive for human immunodeficiency virus.** *Careen Y. Lowder, David M. Meisler, James T. McMahon, David L. Longworth, and Isobel Rutherford,* **242.**

CORRESPONDENCE

Peripheral retinal angiomalike lesion and macular pucker. *Robert Machemer,* **244. Reply.** *Leila Laatikainen, Ilkka Immonen, and Paula Summanen,* **244. Familial congenital cornea guttata with anterior polar cataracts.** *Paolo Nucci,* **245. Reply.** *Elias I. Traboulsi and Richard J. Weinberg,* **245.**

BOOK REVIEWS

Contact Lenses. A Textbook for Practitioner and Student, ed. 3 (Edited by Anthony J. Phillips and Janet Stone). *Reviewed by Barry A. Maltzman,* **246. Guide to Clinical Preventive Services. An Assessment of the Effectiveness of 169 Interventions. Report of the U.S. Preventive Services Task Force (Edited by Michael Fisher).** *Reviewed by Ronald V. Keech,* **246. Pneumatic Retinopexy. A Clinical Symposium (Edited by Paul E. Tornambe and W. Sanderson Grizzard), 247. The 1989 Year Book of Ophthalmology (Edited by Peter R. Laibson), 247.**

ABSTRACTS 248

NEWS ITEMS 254

CLASSIFIEDS . . . . Begins on Advertising 45

COPYRIGHT TRANSFER . . . . Advertising 20

CURRENT ISSUE SUMMARIES . . . . Begins on Advertising 12

INSTRUCTIONS TO AUTHORS . . . . Advertising 35

NEW PRODUCTS AND SERVICES . . . . Begins on Advertising 24

ADVERTISING INDEX . . . . Advertising 50

AMERICAN JOURNAL OF OPHTHALMOLOGY®

VOLUME 109 NUMBER 2 FEBRUARY, 1990

Oral Itraconazole and Topical Miconazole With Débridement for *Acanthamoeba* Keratitis

Yasuhisa Ishibashi, M.D., Yujiro Matsumoto, M.D., Takamichi Kabata, M.D., Ryoko Watanabe, M.D., Sachiko Hommura, M.D., Kazuo Yasuraoka, Ph.D., and Keiich Ishii, Ph.D.

We treated three patients who had *Acanthamoeba* keratitis with oral itraconazole, a new antifungal agent, topical miconazole, and surgical débridement of the lesion. In these patients, healing and regression of the keratitis began six or seven days after initiation of oral itraconazole and miconazole 0.1% eyedrops (every hour during the day). The clinical signs of corneal infection disappeared after nine weeks in Patient 1, after five weeks in Patient 2, and after eight weeks in Patient 3. Visual acuities improved markedly from hand motions to 20/30 in Patient 1, from counting fingers to 20/16 in Patient 2, and from hand motions to 20/40 in Patient 3. In these patients, no systemic or topical signs of toxicity or adverse reactions were noted during the course of treatment.

In 1974, Nagington and associates[1] and in 1975, Jones, Visvesvara, and Robinson[2] described *Acanthamoeba* keratitis for the first time. Since then, *Acanthamoeba* is recognized as an important agent of corneal infection in the United States and Europe. Many reports suggested that contact lens wear and contamination of contact lens solution might be risk factors for *Acanthamoeba* infection.[3-9]

Ophthalmologists have no effective therapy for *Acanthamoeba* keratitis at present, and the prognosis for patients with the disease has been poor. Itraconazole is a new triazole antifungal drug with a broad spectrum.[10] Oral itraconazole is useful for experimental mycosis in various animals.[10] We treated three patients who had *Acanthamoeba* keratitis and wore contact lenses. They were successfully treated with oral itraconazole, topical miconazole, and surgical débridement of the lesion.

Case Reports

Case 1

A healthy 23-year-old man was admitted to the University Hospital of Tsukuba on June 22, 1987, because of ulcerative keratitis in his left eye. He wore daily wear soft contact lenses for the correction of myopia and used homemade solution with tap water. One month earlier, he had worn contact lenses overnight, and on the next morning, the hyperemia and a sensation of a foreign body in the eye appeared. He was treated with topical antibiotics for a corneal abrasion at a contact lens clinic initially, but the symptoms had not resolved. Another ophthalmologist treated him with topical antiviral drugs and topical corticosteroids for presumed herpes simplex keratitis without improvement.

On initial examination, the patient's visual acuity was L.E.: hand motions. A slit-lamp examination of the left eye disclosed a severely inflamed conjunctiva. The left cornea had a

Accepted for publication Oct. 26, 1989.

From the Department of Ophthalmology, Institute of Clinical Medicine (Drs. Ishibashi, Matsumoto, Kabata, Watanabe, and Hommura), the Department of Parasitology, Institute of Basic Medical Sciences (Dr. Yasuraoka), University of Tsukuba, Tsukuba-shi, and the Department of Biology, Hosei University, Tokyo (Dr. Ishii), Japan. This study was supported in part by Grant-in-Aid for Scientific Research (No. 01440086), the Ministry of Education, Science, and Culture of Japan.

Reprint requests to Yasuhisa Ishibashi, M.D., Department of Ophthalmology, Institute of Clinical Medicine, University of Tsukuba, Tsukuba-shi, Ibaraki 305, Japan.

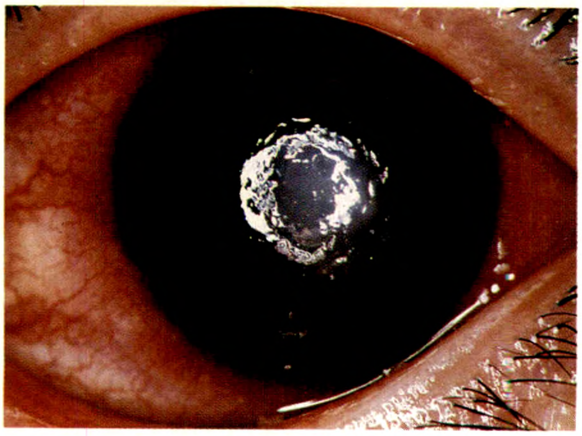


Fig. 1 (Ishibashi and associates). Patient 1, left eye at initial examination. Central round ulcer about 5 mm in diameter occupied one half of the anterior stroma and covered by irregular epithelium.

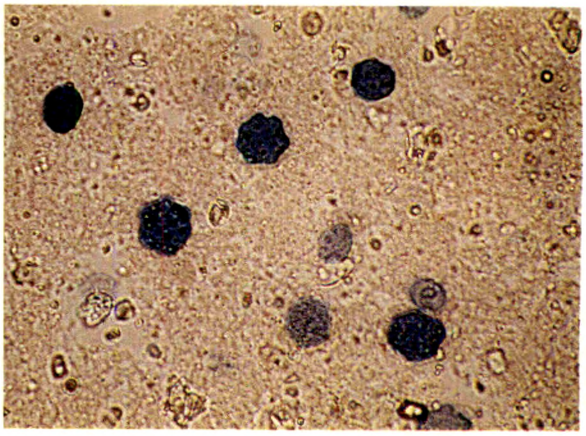


Fig. 2 (Ishibashi and associates). Direct examination of corneal biopsy specimen with ink-potassium hydroxide preparation shows *Acanthamoeba* cysts in the stroma of the lesion (× 400).

central round ulcer about 5 mm in diameter that occupied one half of the anterior stroma and was covered by irregular epithelium (Fig. 1). There was severe reaction in the anterior chamber, but no hypopyon. The patient complained of severe pain, but corneal sensation was decreased. We suspected a fungal keratitis initially; several corneal biopsy specimens were taken from the lesion for direct examination. *Acanthamoeba* cysts (Fig. 2) instead of fungal hyphae were disclosed by direct examination of the specimens with an ink-potassium hydroxide preparation. The cysts were also confirmed by direct examination of corneal scrapings with Gram stain (Fig. 3), Papanicolaou stain (Fig. 4), Giemsa stain, and hematoxylin and eosin stain. Culture of the corneal stroma showed trophozoites (Fig. 5) and cysts of *Acanthamoeba castellanii* and probable *Acanthamoeba polyphaga*. We continued to investigate the exact species of this strain. *Acanthamoeba* species were also isolated from the patient's contact lens solution.

The patient began a regimen of 150 mg of oral itraconazole after breakfast once a day and topical miconazole 0.1% hourly. He underwent surgical débridement of the lesion. Topical miconazole 0.1% was prepared from miconazole 1% in oil for intravenous infusion. We diluted the preparation with saline and put it into a bottle. New solution was made each week. The infection gradually lessened over six or seven days after initiation of the therapy. After ten days, the cornea had totally reepithelialized

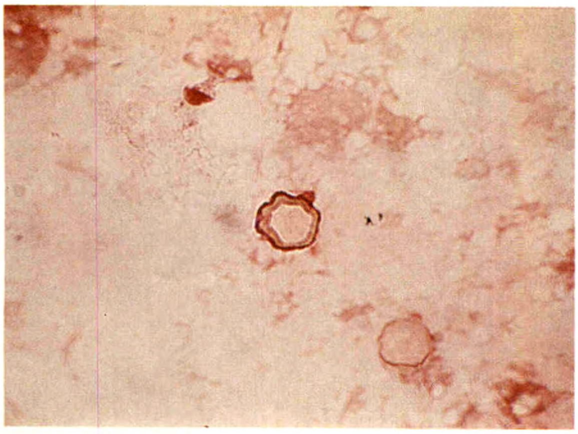


Fig. 3 (Ishibashi and associates). *Acanthamoeba* cysts were confirmed by Gram stain in the corneal scraping (× 400).

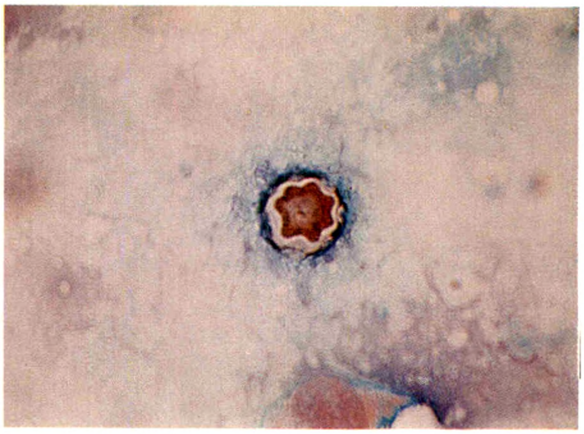


Fig. 4 (Ishibashi and associates). Papanicolaou stain shows *Acanthamoeba* cysts in the corneal scraping of the lesion (× 400).

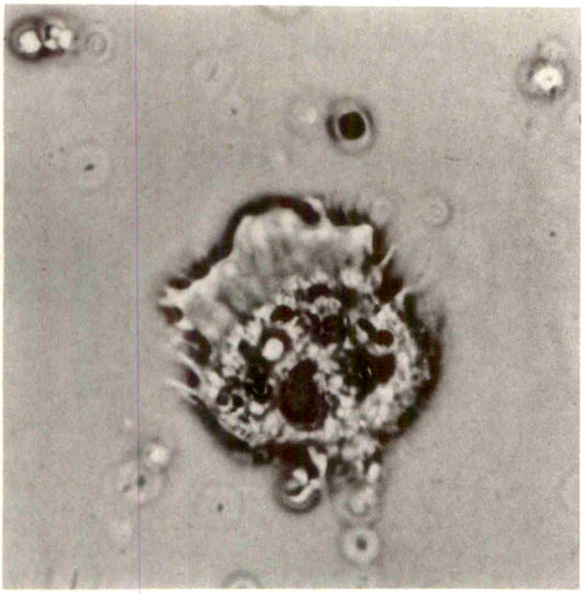


Fig. 5 (Ishibashi and associates). Trophozoites of *Acanthamoeba castellanii* were confirmed by culture of corneal scrapings of the lesion (average axial length, 35 μm).

except for a 3-mm central lesion with moderate infiltration. Because of an improvement, oral itraconazole was reduced to 100 mg/day. Twenty days after the initiation of treatment, visual acuity improved to 20/1,000, and the corneal thickness was almost normal. Oral itraconazole was reduced to 50 mg/day, and topical miconazole was reduced to eight times a day during the day. Visual acuity was 20/70 on July 22 and 20/30 on July 31. The cornea had no epithelial defect at that time. Conjunctival inflammation and reaction of the anterior chamber had also improved. The administration of oral itraconazole (50 mg/day; total, 4,450 mg) and topical miconazole (total, 67 days) stopped on Aug. 31. Mild central corneal opacity remained at the site of infection, but there was no evidence of recurrent infection 19 months after the cessation of the therapy. During the course of the treatment, no systemic or topical signs of toxicity or adverse reaction were noted in this patient.

Case 2

In September 1987, a 19-year-old woman had a conjunctival inflammation and a sensation of a foreign body after removing her daily wear soft contact lenses. An ophthalmologist treated her with topical antibiotic drugs, but her symptoms did not resolve. Another ophthalmologist prescribed topical antiviral drugs and topical corticosteroids for the keratitis for presumed herpes simplex infection, which did not improve. She was referred to us for examination and treatment of the corneal lesion on Oct. 28, 1987.

The patient's visual acuity was L.E.: counting fingers at 10 cm. A slit-lamp examination of the left eye disclosed a mildly inflamed conjunctiva. The left cornea had several scattered subepithelial lesions about 1 mm in diameter centrally. There was moderate reaction in the anterior chamber without hypopyon. There were many folds in Descemet's membrane. Changes in the lens, vitreous body, and fundus were not observed. The right eye had mild myopia.

An ink-potassium hydroxide preparation of the corneal scraping showed *Acanthamoeba* cysts in the corneal stroma. Cultures of the corneal scraping were negative, although cultures of her contact lens solution grew *Acanthamoeba*. The patient entered the hospital on Oct. 29, and began taking oral itraconazole 100 mg/day and topical miconazole 0.1% hourly. Surgical débridement of the lesion was performed as in Patient 1. The lesions started to heal and infiltration decreased after six or seven days of treatment. Intact epithelium covered the lesion, and visual acuity of the left eye returned to 20/30 after two weeks of treatment. Oral itraconazole was reduced to 50 mg/day, and topical miconazole was reduced to eight times per day. On Nov. 20, the left eye had no inflammatory reaction except for the small corneal nebulae with slight conjunctival hyperemia. The visual acuity was 20/16 at this time. Therapy included a total of 3,150 mg of oral itraconazole, 45 days of topical miconazole, and four débridements. No systemic or topical signs of toxicity or adverse reaction of the treatment were observed in this patient.

Case 3

A 37-year-old woman had severe pain and conjunctival inflammation after removing her soft contact lenses on Nov. 13, 1988. She was prescribed topical antibiotics for the corneal ulcer by an ophthalmologist, but her ocular symptoms did not improve. Another ophthalmologist treated her with topical antiviral agents and topical corticosteroids for presumed herpes simplex keratitis without improvement. She entered a hospital and was treated with systemic antiviral drugs and corticosteroids for a few weeks, but the corneal lesion progressed gradually. *Acanthamoeba* cysts were found by

the direct examination of corneal scraping, and *A. castellanii* was cultured from the corneal lesion. The administration of intravenous miconazole and topical natamycin was started immediately after the diagnosis, but the lesion did not respond to these treatments. The patient was referred to us on Feb. 20, 1989, for treatment of *Acanthamoeba* keratitis.

On initial examination, the patient's visual acuity was R.E.: hand motions. A slit-lamp examination of the right eye disclosed a severely inflamed conjunctiva and a central round ulcer about 6 mm in diameter in her right cornea (Fig. 6). The lesion was covered by irregular epithelium. There was severe inflammatory reaction in the anterior chamber with mild hypopyon. The patient complained of a severe pain, which could not be explained by her corneal condition. Direct examination of corneal scrapings with an ink-potassium hydroxide preparation disclosed *Acanthamoeba* cysts. Papanicolaou stain also disclosed cysts in the corneal scraping. Trophozoites and cysts (Fig. 7) of *A. castellanii* were cultured from the corneal scrapings. Oral itraconazole, 200 mg/day (after breakfast), and topical miconazole 0.1%/hour were started immediately, and surgical débridement was performed. The corneal lesion was gradually less infiltrated six or seven days after the initiation of these treatments. After two weeks, the epithelium covered one half of the lesion, and inflammatory reaction had decreased in the anterior chamber. Conjunctival inflammation had also decreased. The patient's visual acuity was R.E.: counting fingers after three weeks of treatment. Oral itraconazole was reduced to 100 mg/day on March 19. The cornea had totally reepithelialized on March 27, five weeks after the initiation of the therapy. The patient had no pain, and the cornea gradually clarified with mild neovascularization. The patient was discharged from the hospital on April 14 and instructed to take 50 mg of oral itraconazole per day and topical miconazole four times a day. Her visual acuity was 20/40 five months after discharge. A total of 6,650 mg of oral itraconazole was administered, and topical miconazole was instilled for 78 days. Surgical débridement of the lesion was performed six times during the patient's hospitalization. During the course of the therapy, no systemic or topical signs of toxicity or adverse reaction were noted in this patient.

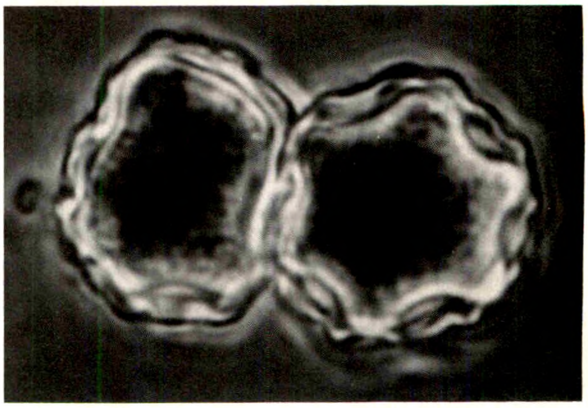


Fig. 7 (Ishibashi and associates). Cysts of *Acanthamoeba castellanii* apparent on the culture of corneal scrapings (average diameter, 14 μm).

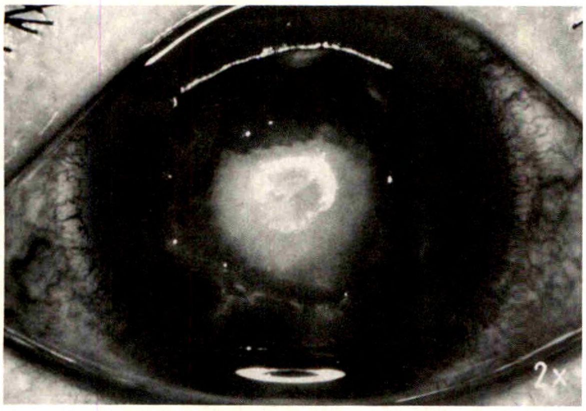


Fig. 6 (Ishibashi and associates). Patient 3, Right eye at initial examination. The right cornea had a central round ulcer, about 6 mm, covered by irregular epithelium.

Discussion

The therapeutic strategy for *Acanthamoeba* keratitis has not been established, although there have been many related published reports. Initially, penetrating keratoplasty was the choice of therapy,[1,2,11-13] but the results were not adequate. The first successful treatment was reported by Wright, Warhurst, and Jones[14] in 1985. Some investigators have reported improvement in *Acanthamoeba* keratitis after the administration of topical neomycin; neomycin combined with bacitracin and polymyxin B; paromomycin; propamidine isethionate; miconazole; and oral ketoconazole. Our choice of

oral itraconazole and topical miconazole with surgical débridement of the lesion seemed to be effective in the treatment of *Acanthamoeba* keratitis in our patients.

Itraconazole is a new triazole with a broad spectrum of activity against many fungal species.[10] The mean plasma concentration after a single 100-mg dose in capsule form is 132 ± 67 ng/ml.[15] Compared to oral ketoconazole, it has fewer side effects.[15] In our three patients, no side effects such as headache, gastrointestinal disturbance, or liver functional disturbance were seen. In Patient 3, the previous ophthalmologist had used intravenous miconazole and topical natamycin for treatment. The patient was treated with 200 mg of intravenous miconazole three times a day (total, 600 mg/day). This dosage was not enough for the treatment of *Acanthamoeba* keratitis. We changed the therapy to oral itraconazole, 200 mg/day, with topical miconazole hourly and surgical débridement. Six or seven days after the change of therapy, the corneal lesion healed gradually. In this patient, the plasma concentration after itraconazole, 200 mg/day for two weeks, was 601 ng/ml. Oral itraconazole was administered once a day, 30 minutes after breakfast, which was convenient for the patients compared to intravenous miconazole, which should be infused three times a day. In combination with topical miconazole and surgical débridement, oral itraconazole appeared to be effective in the treatment of *Acanthamoeba* keratitis. This agent warrants further evaluation for ocular use.

There are many published reports about the staining methods for *Acanthamoeba* keratitis.[16-21] We described the utility of an ink-potassium hydroxide preparation for the diagnosis of fungal keratitis.[22-24] In Patient 1, we initially suspected fungal keratitis from his history and clinical features. Several corneal biopsy specimens were taken from the margin of the lesion and immediately examined with an ink-potassium hydroxide preparation by photomicroscopy. We found round, double-walled cysts instead of fungal hyphae. We also used Gram stain, Giemsa stain, Papanicolaou stain, and hematoxylin and eosin stain. All stains showed amebic cysts.

Surgical débridement has been used for the treatment of herpes simplex keratitis, especially the epithelial type, and for fungal keratitis. Holland and Donzis[25] described the utility of epithelial débridement for early *Acanthamoeba* keratitis. We considered surgical débridement useful for the diagnosis, improvement of drug penetration for the cornea, and removal of pathogens from the lesion. In the treatment of *Acanthamoeba* keratitis, we believe that surgical débridement is effective in combination with systemic and topical drugs, because although trophozoites are sensitive to several drugs, amebic cysts are resistant to drugs.

References

1. Nagington, J., Watson, P. O., Playfair, T. G., McGill, J., Jones, B. R., and Steele, A. D.: Amoebic infection of the eye. Lancet 2:1537, 1974.
2. Jones, D. B., Visvesvara, G. S., and Robinson, N. M.: *Acanthamoeba polyphaga* keratitis and *Acanthamoeba* uveitis associated with fatal meningoencephalitis. Trans. Ophthalmol. Soc. U.K. 95:221, 1975.
3. Hirst, L. W., Green, W. R., Merz, W., Kaufman, C., Visvesvara, G. S., Jensen, A., and Howard, M.: Management of *Acanthamoeba* keratitis. A case report and review of the literature. Ophthalmology 91:1105, 1984.
4. Moore, M. B., McCulley, J. P., Luckenbach, M., Gelender, H., Newton, C., McDonald, M. B., and Visvesvara, G. S.: *Acanthamoeba* keratitis associated with soft contact lenses. Am. J. Ophthalmol. 100:396, 1985.
5. Cohen, E. J., Buchanan, H. W., Laughrea, P. A., Adams, C. P., Galentine, P. G., Visvesvara, G. S., Folberg, R., Arentsen, J. J., and Laibson, P. R.: Diagnosis and management of *Acanthamoeba* keratitis. Am. J. Ophthalmol. 100:389, 1985.
6. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. (Case 10-1985). N. Engl. J. Med. 312:634, 1985.
7. Cohen, E. J., Parlato, C. J., Arentsen, J. J., Genvert, G. I., Eagle, R. C., Wieland, M. R., and Laibson, P. R.: Medical and surgical treatment of *Acanthamoeba* keratitis. Am. J. Ophthalmol. 103:615, 1987.
8. Jones, D. B.: *Acanthamoeba*—the ultimate opportunist? Am. J. Ophthalmol. 102:527, 1986.
9. Stehr-Green, J. K., Bailey, T. M., Floy, H. B., Carr, J. H., Bond, W. W., and Visvesvara, G. S.: *Acanthamoeba* keratitis in soft contact lens wearers. A case-control study. JAMA 258:57, 1987.
10. Van Cutsem, J., Van Gerven, F., and Janssen, P. A. J.: The in vitro and in vivo antifungal activity of itraconazole. In Fromtling, R. A. (ed.): International Telesymposium on Recent Trends in the Discovery, Development and Evaluation of Antifungal Agents. Beerse, Belgium, J. R. Prous Science, 1987, p. 177.
11. Lund, O. E., Stefani, F. H., and Dechant, W.: Amoebic keratitis. A clinicopathological case report. Br. J. Ophthalmol. 62:373, 1978.

12. Bos, H. J., Volker-Dieben, H. J. M., and Kok-van Alphen, C. C.: A case of *Acanthamoeba* keratitis in the Netherlands. Trans. R. Soc. Trop. Med. Hyg. 75:86, 1981.

13. Ma, P., Willaert, E., Juechter, K. B., and Stevens, A. R.: A case of keratitis due to *Acanthamoeba* in New York, New York, and features of 10 cases. J. Infect. Dis. 143:622, 1981.

14. Wright, P., Warhurst, D., and Jones, B. R.: *Acanthamoeba* keratitis successfully treated medically. Br. J. Ophthalmol. 69:778, 1985.

15. Heykants, J., Michiels, M., Meuldermans, W., Monbaliu, J., Lavrijsen, K., Van Peer, A., Levron, J. C., Woestenborghs, R., and Cauwenbergh, G.: The pharmacokinetics of itraconazole in animals and man. An overview. In Fromtling, R. A. (ed.): International Telesymposium on Recent Trends in the Discovery, Development and Evaluation of Antifungal Agents. Beerse, Belgium, J. R. Prous Science, 1987, p. 223.

16. Margo, C. E., Brinser, J. H., and Groden, L.: Exfoliated cytopathology of *Acanthamoeba* keratitis. JAMA 255:2216, 1986.

17. Epstein, R. J., Wilson, L. A., Visvesvara, G. S., and Plourde, E. G., Jr.: Rapid diagnosis of *Acanthamoeba* keratitis from corneal scrapings using indirect fluorescent antibody staining. Arch. Ophthalmol. 104:1318, 1986.

18. Wilhelmus, K. R., Osato, M. S., Font, R. L., Robinson, N. M., and Jones, D. B.: Rapid diagnosis of *Acanthamoeba* keratitis using calcofluor white. Arch. Ophthalmol. 104:1309, 1986.

19. Marines, H. M., Osato, M. S., and Font, R. L.: The value of calcofluor white in the diagnosis of mycotic and *Acanthamoeba* infections of the eye and ocular adnexa. Ophthalmology 94:23, 1987.

20. Silvany, R. F., Luckenbach, N. W., and Moore, M. B.: The rapid detection of *Acanthamoeba* in paraffin-embedded sections of corneal tissue with calcofluor white. Arch. Ophthalmol. 105:1366, 1987.

21. Robin, J. B., Chan, R., and Andersen, B. R.: Rapid visualization of *Acanthamoeba* using fluorescein-conjugated lectins. Arch. Ophthalmol. 106:1273, 1988.

22. Arffa, R. C., Avni, I., Ishibashi, Y., Robin, J., and Kaufman, H. E.: Calcofluor and ink-potassium hydroxide preparations for identifying fungi. Am. J. Ophthalmol. 100:719, 1985.

23. Ishibashi, Y., and Kaufman, H. E.: Corneal biopsy in the diagnosis of keratomycosis. Am. J. Ophthalmol. 101:288, 1986.

24. Ishibashi, Y., Hommura, S., and Matsumoto, Y.: Direct examination vs culture of biopsy specimens for the diagnosis of keratomycosis. Am. J. Ophthalmol. 103:636, 1987.

25. Holland, G. N., and Donzis, P. B.: Rapid resolution of early *Acanthamoeba* keratitis after epithelial débridement. Am. J. Ophthalmol. 104:87, 1987.

OPHTHALMIC MINIATURE

A house of sleeping humans is both closed and wide open. Like an ear it resists easy penetration but cannot brace for attack. Luckily in the Caribbean there is no fear. The unsocketed eye that watches sleepers is not threatening—it is merely alert, which anyone can tell for it has no lid and cannot wax or wane.

Toni Morrison, *Tar Baby*
New York, New American Library, Inc., 1983, p. 36

Ocular Infections Associated With *Eikenella corrodens*

Betty Klein, M.D., Jeffrey Couch, M.D., and John Thompson, M.D.

Eikenella corrodens **is a gram-negative, facultative rod-shaped anaerobe that colonizes the human mouth, nasopharynx, gut, and genitourinary tract. We treated a corneal ulcer from which *E. corrodens* was the primary isolate in an otherwise healthy man. We treated another patient who had recurrent bacterial endophthalmitis from which *Eikenella* was identified in mixed culture. Named for its ability to form pits in agar, the corroding bacillus is gaining recognition for its role in head and neck infections. Certain *E. corrodens* strains are mobile on moist surfaces and elaborate an endotoxin, which may destroy human tissues directly and indirectly by means of the immune system. The organism is usually resistant to aminoglycosides and penicillinase-resistant penicillins yet is susceptible to penicillin and some cephalosporins.**

Eikenella corrodens is a gram-negative, facultative anaerobic rod-shaped organism that may be normal flora in the human mouth, nasopharynx, gut, and genitourinary tract. This corroding bacillus is a newly recognized human pathogen with an increasing role in head and neck infections.[1-3] In 1988, Dua and associates[4] reported a case of recurrent lacrimal abscess caused by *E. corrodens*. A report of two cases of orbital cellulitis in 1979[5] and a report of two cases of conjunctivitis and one of dacryocystitis in 1986[6] confirm the potential of this organism to cause ocular adnexal disease. In our experience, *E. corrodens* was the primary isolate from a corneal ulcer in an otherwise healthy man. We studied another case of bacterial endophthalmitis related to trauma from which *Eikenella* was isolated in mixed culture. A review of published reports has disclosed several unique characteristics that may influence the effect of the corroding bacillus on the eye as well as the management of these conditions.

Accepted for publication Oct. 12, 1989.
From the Yale Eye Center for Clinical Research, New Haven, Connecticut.
Reprint requests to Betty Klein, M.D., Yale Eye Center for Clinical Research, 330 Cedar St., P.O. Box 3333, New Haven, CT 06510.

Case Reports

Case 1

A 58-year-old man had a three-day history of a painful right eye. On the day before his symptoms, he had been cutting tree branches and thought he had gotten something in his eye. His only medical condition consisted of a seizure disorder for which he took 100 mg of phenytoin three times daily for 20 years. His visual acuity was R.E.: hand motions and L.E.: 20/30. Mild right upper and lower eyelid edema was present, and the conjunctiva was red and chemotic. There was a 1- to 2-mm area of stromal haze and epithelial defect in the inferior paracentral cornea (Fig. 1), which was surrounded by a 4-mm area of clear but edematous cornea. The remainder of the cornea had only trace edema. Bowman's membrane was intact. No flare or cell was seen in the anterior chamber, the iris was normal, and the lens and anterior vitreous were clear. Ophthalmoscopy showed mild pigmentary changes in the peripheral retina, but the findings were otherwise normal. After obtaining corneal scraping for culture, an hourly regimen of 14 mg/ml of gentamicin alternating with 50 mg/ml of cefazolin was instituted. Gram stain was negative. *Eikenella corrodens* grew in multiple colonies on multiple plates from the corneal ulcer scraping (Fig. 2). The organism was sensitive to cefazolin, tobramycin, chloramphenicol, penicillin, and ampicillin but resistant to metronidazole, clindamycin, gentamicin, and lincomycin.

One week after the initial examination, the patient was transferred to the cornea service at Yale-New Haven Hospital. The ulcer had grown to 3 mm in diameter and had eroded through Bowman's membrane, which was intact after the corneal scraping. Mucinous debris plugged

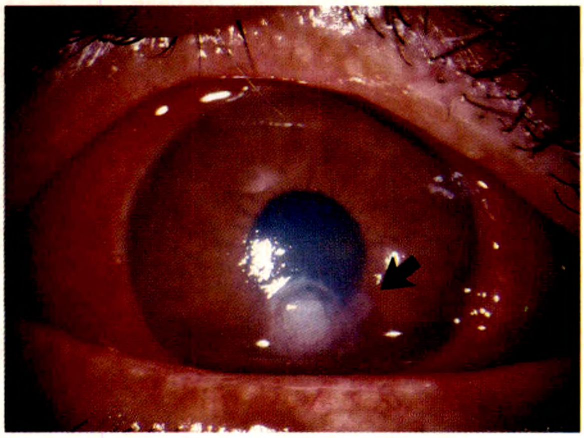


Fig. 1 (Klein, Couch, and Thompson). Corneal ulcer, satellite lesion (arrow).

the epithelial defect, which was surrounded by 0.5 mm of inflammatory infiltrate. A small satellite lesion was seen contiguous to the superonasal border of the ulcer. The anterior chamber contained moderate (2+) ray and cell but no keratic precipitates or hypopyon. The patient described the pain, which was considerable, as "stinging." Stains for bacteria and a mycology smear were negative. The ulcer was cultured and then recultured 24 hours after the termination of antibiotics, and a regimen of topical tobramycin, 15 mg/ml per hour, was begun. The course was complicated by a unilateral pressure rise in the right eye to 38 mm Hg, which was treated with topical timolol 0.5% twice daily and 250 mg of oral acetazolamide four times daily. The infiltrate and epithelial edema began to decrease four days after the transfer (ten days after the initial examination). Re-epithelialization and clearing of the infiltrate progressed slowly. The patient was discharged 15 days after the initial examination and put on a regimen of topical chloramphenicol and dexamethasone, the epithelial defect having healed. The second set of bacterial cultures yielded a trace (1+) growth of *Propionibacterium acnes* susceptible to ampicillin, cephalothin, chloramphenicol, clindamycin, erythromycin, penicillin, tetracycline, and cefotetan and resistant only to metronidazole after seven days of culture. Viral cultures were negative.

Case 2

An 18-year-old man was cutting wire when a small piece hit his right eye. He was seen the same day and taken to surgery for what was believed to be a corneal laceration. He was hospitalized and treated overnight with intravenous ampicillin. The patient was discharged and put on a regimen of topical antibiotics, atropine and prednisone acetate. Two days later, he noted a yellowish discharge from the eye and increasing pain. The diagnosis of endophthalmitis was made, and he was referred to the retina service of Yale-New Haven Hospital for possible pars plana vitrectomy.

The patient's best-corrected visual acuity was R.E.: light perception with projection and L.E.: 20/20. The right upper and lower eyelids were erythematous and swollen. The right conjunctiva was injected. There was a purulent exudate from the right corneal wound superiorly, and diffuse corneal edema. Marked cell and flare

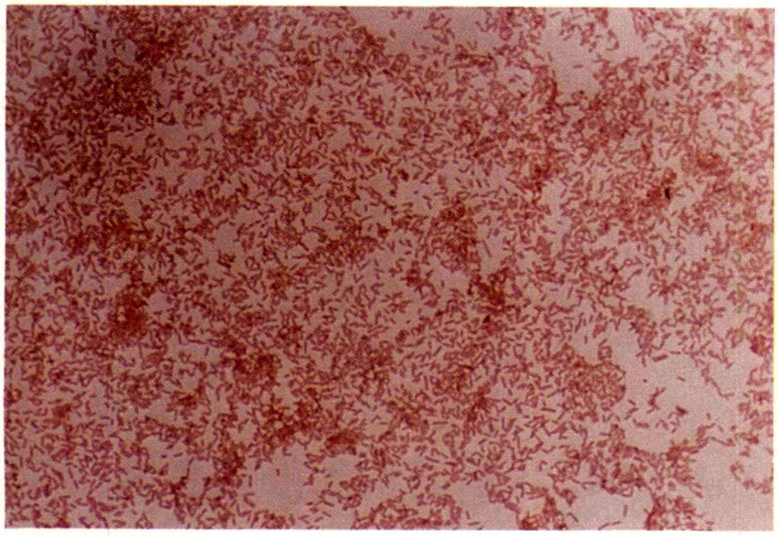


Fig. 2 (Klein, Couch, and Thompson). *Eikenella corrodens*, a facultative gram-negative bacillus (gram stain, $\times$ 3,000).

was noted in the anterior chamber, but there was no hypopyon. The anterior segment of the left eye was normal. Applanation tensions were 12 mm Hg in the right eye and 16 mm Hg in the left eye. The right fundus was not visible. The left fundus showed normal vessels, macula, optic nerve, and periphery. The patient was afebrile with a white blood cell count of 11.6 cells/mm^3. He was admitted to the hospital and treated with intravenous cefazolin and gentamicin sulfate. A computed tomographic scan disclosed no intraocular foreign body. A gram stain of the exudate from the corneal wound was negative for organisms or white blood cells. The patient was brought to the operating room on the same day for anterior chamber washout, pars plana vitrectomy, and instillation of 2.5 mg of intravitreal cefazolin and 100 μg of gentamicin. Postoperatively, the patient had brisk perception of light in the right eye. A fibrinous white membrane was adherent to the anterior surface of his iris, obscuring the lens and posterior segment. The same intravenous antibiotics were continued and 60 mg of oral prednisone per day and topical prednisolone acetate four times daily were started. Over the next three days, he had decreasing pain but persisting fibrinous reaction in the anterior chamber, which obscured the lens. The intraocular pressure of the right eye increased to 38 mm Hg, and it was treated with timolol. Culture of the vitreous aspirate grew many (3+) beta-*Streptococcus* species, many (4+) *Capnocytophaga* species, many (4+) *Staphylococcus aureus*, and many (4+) alpha-*Streptococcus* species. The patient was discharged from the hospital and instructed to take 250 mg of oral cephalexin four times daily and apply fortified topical gentamicin (15 mg/ml) and fortified cefazolin (50 mg/ml) four times daily to the right eye. The corticosteroids were continued as previously.

The patient returned nine days after surgery because of throbbing pain in the right eye. He had moderate (2+) conjunctival injection, trace corneal edema, marked (3+) ray and mild (1+) cell in the anterior chamber, engorged iris vessels, and an opaque cataractous lens. Applanation tension was 26 mm Hg in the right eye. Gonioscopy disclosed a transillumination defect in the iris under the corneal laceration site. The fundus was not visible. B-scan ultrasonography disclosed many internal echoes in the vitreous corresponding to inflammation and a central clear area corresponding to the previous vitrectomy. The patient was taken to the operating room for a repeat vitrectomy. During the procedure, gross pus was noted throughout the vitreous cavity. Organized inflammatory exudate was adherent to the optic nerve and macula, and a retinal detachment was noted in the periphery. The detachment was repaired by laser endophotocoagulation and cryopexy with fluid-gas exchange. *Staphylococcus aureus*, *Capnocytophaga* species, and *E. corrodens* grew in cultures of the aspirate from repeat vitrectomy. All of the organisms were sensitive to the antibiotics used in the first vitrectomy.

Discussion

In 1958, Eiken applied the name *Bacteroides corrodens* to an anaerobic gram-negative bacillus, which formed pits in agar.[7] Some of the *B. corrodens* strains grew in both aerobic and anaerobic environments. These facultative strains were demonstrated by Jackson and associates[8] in 1970 to be biochemically and genetically unique from the obligately anaerobic *Bacteroides* species and were reclassified under the new genus *Eikenella corrodens*.[9]

Eikenella species are found in the human mouth and commonly appear in orally contaminated wounds.[6] They have, however, been the sole organisms isolated from a case of fatal bacterial endocarditis,[1] ten cases of bacteremia, and more than six cases of brain abscess, subdural abscess, and meningitis.[1,2,10] A newly recognized pathogen, *Eikenella* is demonstrating an increasing role in infections of the head and neck[3] as well as of the ocular adnexa.[4] The organism is not considered normal conjunctival flora. Dua and associates[4] inoculated swabs from the conjunctiva of 40 healthy volunteers onto blood agar supplemented with clindamycin. After 72 hours of incubation, none of the cultures were found to contain *E. corrodens*.

Eikenella corrodens strains are usually susceptible to penicillin G, ampicillin, tetracycline, cefoxitin, cefotaxime, chloramphenicol, and some beta-lactam antibiotics.[3,11,12] Cefazolin is reported to be consistently effective.[13] Strains are often resistant to penicillinase-resistant penicillins, such as dicloxacillin and oxacillin, and are variably sensitive to cephalothin, cephapirin, and cephaloridine.[13,14] Resistance to aminoglycosides is variable, but the organism is usually resistant to gentamicin.[2,3,14] Constant features are resistance to clindamycin, linco-

mycin, and metronidazole; empiric treatment of known or suspected *E. corrodens* infection with these agents is inappropriate.[3,12] The antibiotic sensitivities discussed above are based on the experience of a number of different laboratories working with *Eikenella* from a variety of infections and can serve at best as a rough guide. The importance of serial dilution sensitivity testing is highlighted in a recent report of a beta-lactamase producing strain of *E. corrodens* from an intra-abdominal abscess.[15] Disk sensitivity testing is thought to be less reliable for this organism.[3]

Eikenella corrodens grows best on blood or chocolate agar incubated with 5% to 15% CO_2 at 35 to 37 C both anaerobically and aerobically.[3,16] It may take 24 to 48 hours for the small grayish pitting colonies to be recognized.[3] Clindamycin (0.5 μg/ml) will facilitate isolation from mixed infections. It may be useful to note that this slow-growing, fastidious organism is sometimes overgrown in initial cultures only to be isolated after the use of antibiotics for which *Eikenella* is resistant.[6] Initial cultures from the corneal ulcer in Patient 1 grew *E. corrodens* alone and on multiple dishes. The 1+ growth of *P. acnes* after seven days of culture from the second specimen collected from this patient after one week of antibiotic therapy does not dissuade us from considering *E. corrodens* to be the primary organism involved in this infection. The growth of *Eikenella* from the vitreous in Patient 2 demonstrates that *Eikenella* can occur in the setting of a polymicrobial endophthalmitis.

Eikenella corrodens should be considered a possible agent in ocular infections. Despite intensive application of appropriate topical antibiotics, the corneal ulcer of Patient 1 grew for ten days before any sign of improvement. Additionally, a satellite lesion developed at the margin of the ulcer after one week of therapy. The host pathogen interaction for the corroding bacillus has never been studied in the eye, but experimental work in the periodontal literature[17] suggests important immunologic and nonimmunologic roles of *E. corrodens* endotoxin in bone and tissue destruction. Some corroding strains have been observed microscopically in a form of surface translocation known as "twitching motility," which consists of a series of irregular jerks capable of generating speeds of 1 to 5 μm/min and is dependent on the presence of a film of water on the surface of the medium.[16] The appearance of a satellite ulcer and the initial worsening of our patient's corneal ulcer while on antibiotic therapy may represent the organism's ability to spread on moist surfaces and the effect of the endotoxin, respectively.

Many published reports about *E. corrodens* are devoted to the organism's unusual pattern of antibiotic sensitivity—it is sensitive to penicillin and some cephalosporins but variably resistant to aminoglycosides and penicillinase-resistant penicillins. *Eikenella corrodens* was not considered a pathogen before 1970. As the number of infections with *E. corrodens* as the sole isolate grew, the organism gained recognition as an emerging pathogen of the head and neck, respiratory tract, central nervous system, abdominal and joint spaces, and flesh wounds. This may reflect an increase in the use of aminoglycoside and penicillinase-resistant penicillins, which can render this organism the sole survivor from a mixed infection. If this is a trend, additional ocular infections with this uncommon organism may soon appear. In many centers, initial empiric therapy for bacterial endophthalmitis consists of subconjunctival and intravenous gentamicin coupled with a penicillinase-resistant penicillin. This therapy may be inadequate for endophthalmitis related to trauma with possible oral or nasopharyngeal contamination. No specific history of contamination from these areas was offered by the patients described herein; however, hand-to-eye transmission remains a possibility.

References

1. Dorff, G. J., Jackson, L. J., and Rytel, M. W.: Infections with *Eikenella corrodens*. A newly recognized human pathogen. Ann. Intern. Med. 80:305, 1974.

2. Suwanagool, S., Rothkopf, M. M., Smith, S. M., LeBlanc, D., and Eng, R.: Pathogenicity of *Eikenella corrodens* in humans. Arch. Intern. Med. 143:2265, 1983.

3. Tami, T. A., and Parker, G. S.: *Eikenella corrodens*. An emerging pathogen in head and neck infections. Arch. Otolaryngol. 110:752, 1984.

4. Dua, H. S., Paterson, A., Smith, F. W., Scott, G. B., and Forrester, J. V.: Recurrent lacrimal abscess caused by *Eikenella corrodens*. Am. J. Ophthalmol. 106:237, 1988.

5. Schwartz, H., Baskin, M. A., Ilkiw, A., and LeBeau, L.: An unusual organism causing orbital cellulitis. Br. J. Ophthalmol. 63:710, 1979.

6. Stoloff, A. L., and Gillies, M. L.: Infections with

Eikenella corrodens in a general hospital. A report of 33 cases. Rev. Infect. Dis. 8:50, 1986.

7. Eiken, M.: Studies on an anaerobic, rod-shaped, gram-negative microorganism. *Bacteroides corrodens* n. sp. Acta Pathol. Microbiol. Scand. 43:404, 1958.

8. Jackson, F. L., Goodman, Y. E., Bel, F. R., Wong, P. C., and Whitehouse, R. L. S.: Taxonomic status of facultative and strictly anaerobic "corroding bacilli," that have been classified as *Bacteroides corrodens*. J. Med. Microbiol. 4:171, 1971.

9. Henriksen, S. D.: Corroding bacteria from the respiratory tract. 2. *Bacteroides corrodens*. Acta. Pathol. Microbiol. Scand. 75:91, 1969.

10. Marsden, H. B., and Hyde, W. A.: Isolation of *Bacteroides corrodens* from infections in children. J. Clin. Pathol. 24:117, 1971.

11. Goldstein, E. J. C., Gombert, M. E., and Agyare, E. O.: Susceptibility of *Eikenella corrodens* to newer beta-lactam antibiotics. Antimicrob. Agents Chemother. 6:543, 1974.

12. Robinson, J. V. A., and James, A. L.: In vitro susceptibility of *Bacteroides corrodens* and *Eikenella corrodens* to ten chemotherapeutic agents. Antimicrob. Agents Chemother. 6:543, 1974.

13. Goldstein, E. J. C., Sutter, V. L., and Finegold, S. M.: Susceptibility of *Eikenella corrodens* to the cephalosporins. Antimicrob. Agents Chemother. 14:639, 1978.

14. Konugres, G. S., Goldstein, E. J. C., and Wallace, S. L.: *Eikenella corrodens* as a cause of osteomyelitis in the feet of diabetic patients. J. Bone Joint Surg. Am. 69A:940, 1987.

15. Trallero, E. P., Arenzana, J. M. G., Eguiluz, G. C., and Larrucea, J. T.: β-Lactamase-producing *Eikenella corrodens* in an intraabdominal abscess. J. Infect. Dis. 153:379, 1986.

16. Jackson, F. L., and Goodman, Y.: Genus *Eikenella*. In Krieg, W. R., and Holt, J. G. (eds.): Bergey's Manual of Systemic Bacteriology, vol. 1. Baltimore, Williams and Wilkins, 1983, pp. 591–597.

17. Johnson, D. A., Behling, U. H., Listgarten, M., and Nowatny, A.: Role of bacterial products in peridontitis. Humoral immunologic response to *Eikenella corrodens*. Infect. Immun. 22:382, 1978.

Ophthalmic miniature

There had been so many parts of the body to choose from....The eye, for instance. She'd always been fond of the structure of the eye. She liked the way it sat so obediently in its socket and the way it came in colors. She liked the fact you could see all the way to a person's brain. But in the end some of the problems of the eye upset her. Once during her ophthalmology rotation, she tried making dinner with her eyes closed.

Mary Morris, *The Waiting Room*
New York, Doubleday, 1989, p. 6

Cyclosporine-Containing Collagen Shields Suppress Corneal Allograft Rejection

Y. F. Chen, M.D., B. M. Gebhardt, Ph.D., J. J. Reidy, M.D., and H. E. Kaufman, M.D.

Thirty-seven rabbit eyes with penetrating keratoplasty grafts placed in vascularized beds to enhance the possibility of graft rejection were treated with cyclosporine delivered in collagen shields or drops of olive oil. Treatment was begun either immediately after grafting or at the first sign of immune graft reaction. Mean survival time of the grafts in the collagen shield treated eyes was significantly longer than in the eyes treated with drops. In the eyes treated at the first sign of graft reaction, cyclosporine in collagen shields halted the rejection process; seven of these eyes survived the 120-day observation period, compared to one of the eyes treated with drops. These results indicate that the collagen shield is an effective delivery system for cyclosporine and that topically administered cyclosporine is effective in suppressing the initiation of graft rejection and in reversing a graft reaction in progress.

THE TOPICAL AND ORAL administration of cyclosporine has recently been reported to be a valuable adjunct to corticosteroids in patients with a high risk of rejection after corneal transplantation. Belin and associates[1] reported that 2% cyclosporine in combination with corticosteroid drops yielded 91% clear, surviving corneal allografts in patients thought to be at high risk for graft rejection. Hill[2] found that the combination of oral cyclosporine and topical and systemic corticosteroids was a significantly more effective drug regimen for the prevention of corneal allograft rejection in patients at high risk, compared to topical or topical and systemic corticosteroids alone. The goal of our study was to determine if collagen shield delivery would enhance the efficacy of cyclosporine for preventing or reversing graft rejection in an animal model of high-risk penetrating keratoplasty.

Previously, we demonstrated that collagen shields containing cyclosporine delivered consistently high levels of the drug to the cornea and measurable levels of the drug to the anterior chamber in normal, unoperated rabbit eyes.[3] The availability of a drug delivery system that provides a high concentration of cyclosporine to the cornea with the application of a small amount of drug offers a new approach to the treatment of graft rejection in the eye. Topical application of cyclosporine should minimize the systemic side effects, but there is no evidence that this drug, which blocks antigen-stimulated T-cell activation, can act locally on T cells after they have been recruited from the lymphoid tissue or blood.

In this study, we evaluated topical cyclosporine delivered by collagen shield for the capacity to prevent the initiation of a primary corneal allograft reaction or to reverse an ongoing allograft reaction in heavily vascularized grafts in rabbit eyes. We considered it important to determine if locally administered cyclosporine can prevent T-cell recruitment and activation, which are initial steps in the allograft reaction, even though these events may occur in the lymphoid tissues.

Accepted for publication Oct. 26, 1989.

From the Lions Eye Research Laboratories, LSU Eye Center, Louisiana State University Medical Center School of Medicine, New Orleans, Louisiana. This study was supported in part by Public Health Service grants EY03150, EY02580, and EY02377 from the National Eye Institute, National Institutes of Health, Bethesda, Maryland. This study was presented in part as a poster at the annual meeting of the Association for Research in Vision and Ophthalmology, May 1, 1989, Sarasota, Florida. Drs. Gebhardt and Kaufman are paid consultants to Bausch and Lomb, the manufacturers of the collagen shields, and Sandoz, the manufacturers of cyclosporine used in this study. None of the other authors have any financial or proprietary interest in either company.

Reprint requests to Bryan M. Gebhardt, Ph.D., LSU Eye Center, 2020 Gravier St., Suite B, New Orleans, LA 70112.

Material and Methods

We used 108 young adult New Zealand white rabbits of both sexes, weighing 3 to 5 lbs. each, as donors and recipients of penetrating corneal allografts. The animals were maintained and handled in accordance with the ARVO Resolution on the Use of Animals in Research.

A high-risk keratoplasty model recently described by Hill and Maske[4] was used to ensure a high incidence of corneal allograft reactions. In this model, corneal vascularization was induced with silk sutures, resulting in the rejection of a high percentage of allografts placed in the vascularized graft sites.[4]

In our study, rabbits that were to be recipients of corneal allografts were anesthetized with a mixture of ketamine hydrochloride at a concentration of 30 mg/kg of body weight, xylazine hydrochloride at a concentration of 3 mg/kg of body weight, and atropine at 0.04 mg/kg of body weight. Corneal vascularization was induced by placing 6-0 silk sutures in the upper 180 degrees of the cornea to a depth of approximately one half to two thirds the thickness of the cornea. Two weeks later, when the upper half of the cornea was vascularized, the sutures were removed and penetrating keratoplasty was performed.

One drop each of 1% atropine sulfate ophthalmic solution and 2.5% phenylephrine ophthalmic solution was placed on the eye to be grafted just before surgery. The surgical field of the eye was protected with a sterile surgical drape. Two 6-0 bridle sutures, one placed inferotemporally and one superotemporally, were used to stabilize the globe. The graft site of the recipient was prepared by partial trephination with a 7-mm disposable trephine. Controlled entry into the anterior chamber was made with a No. 11 stainless steel (Bard-Parker) blade. The cornea was removed from the recipient eye, and two drops of a 1:5,000 dilution of sodium heparin were instilled into the open anterior chamber. A 7.5-mm diameter corneal allograft from an unrelated rabbit was used as the graft. The allograft donors were killed by sodium pentobarbital overdose and the graft obtained as above. The penetrating graft was secured in position with four interrupted 10-0 nylon sutures. A 16-bite running 10-0 nylon suture was then used to fix the graft in place. The cardinal sutures were removed, and one drop each of 1% atropine ophthalmic solution and neomycin-gramicidin-polymixin B ophthalmic solution was placed onto each eye. The anterior chamber was reformed with a viscoelastic agent (Healon). The rabbits were observed during the postoperative period to ensure that recovery from anesthesia was uneventful. Control autografts were performed in the same manner except that a 7.5-mm corneal button was removed, rotated 180 degrees, and returned to the donor eye.

All animals were observed daily by slit-lamp biomicroscopy, and the condition of the graft was noted. Grafts that failed for technical reasons were excluded from further study.

To confirm the results of Hill and Maske,[4] we compared the survival of corneal allografts placed in graft sites that had been vascularized with silk suture implants with the survival of grafts in normal, nonvascularized eyes. Thirty rabbits were used as graft recipients in this phase of the study. Seventeen eyes with vascularized beds and eight normal eyes underwent penetrating keratoplasty. Five normal eyes underwent autotransplantation. The eyes were examined by slit-lamp microscopy twice weekly for 120 days, and the time to complete immune rejection was recorded.

Collagen shields containing 4 mg of cyclosporine were prepared by Bausch & Lomb Pharmaceuticals. Sterile porcine collagen was placed into contact lens molds having a base curve of 9.0 mm and a diameter of 14.5 mm. Each 0.8 ml of collagen contained 4 mg of crystalline cyclosporine. Under conditions of controlled temperature and humidity, the collagen was allowed to dehydrate to form a thin film. The collagen shields were sterilized by exposure to approximately 20,000 Gy (2 megarads) of gamma irradiation from a cobalt 60 source. In vitro dissolution studies established that the average time of the shields used in this study was 24 hours.

Crystalline cyclosporine was mixed with USP grade olive oil at a concentration of 10 mg of cyclosporine per milliliter of olive oil. The mixture was warmed to 37 C until the cyclosporine dissolved completely. The solution was sterilized by passage through a 0.45-μm filter and stored in sterile dropper bottles for administration to rabbit eyes. The concentration of cyclosporine in the final preparation was confirmed by radioimmunoassay. The gentle warming and filtration caused no measurable loss of drug.

Animals were killed when their allografts were considered to have undergone irreversible immune rejection or at the end of the study (120

days after grafting). Corneas were excised and placed into Michel's immunofixative for short-term storage. The tissue was then frozen in optimum cutting temperature (OCT) compound and 6-μm thick cryostat sections were prepared. The sections were fixed in cold acetone and incubated separately in monoclonal antibodies specific for rabbit T-lymphocytes (clone L11/135[6]) or a monoclonal antibody specific for the rabbit class II histocompatibility antigen (clone 2C4[6]). Identification of cells bearing T-lymphocyte marker or class II marker was accomplished using a commercially available avidin-biotin complex immunoperoxidase staining kit. The tissue sections were first incubated in methyl alcohol containing 0.3% hydrogen peroxide for 30 minutes and rinsed in phosphate-buffered saline, pH 7.2. The sections were then incubated in 0.1% horse serum, gently blotted, and incubated for 30 minutes in undiluted tissue culture supernatant containing either the anti-T cell or anti-class II monoclonal antibody. After this incubation, the sections were rinsed in phosphate-buffered saline for three five-minute intervals and then incubated in a 0.1% biotinylated horse-anti-mouse immunoglobulin for 30 minutes. The sections were again rinsed in phosphate-buffered saline and incubated for 60 minutes in a 0.5% solution of the avidin-biotin peroxidase complex and rinsed again in three changes of phosphate-buffered saline. Finally, the sections were incubated for ten minutes in a solution of 3',3-diaminobenzidine/hydrogen peroxide (10 mg of diaminobenzidine in 10 ml of phosphate-buffered saline, 50 μl of 8% nickel chloride, and 10 μl of 30% hydrogen peroxide). The sections were washed in three changes of phosphate-buffered saline and counterstained in 0.1% methyl green in 0.2 N acetate buffer, dehydrated in absolute alcohol, cleared in toluene, and coverslipped.

The clinical evaluation of the corneal allograft reaction was standardized by use of a grading system. Grade 0 allografts were those that failed to exhibit vascularization, cloudiness, or edema. Grade 1 allografts exhibited a faint corneal haze and mild infiltrative vascularization at the original site of placement of the silk sutures. Grade 2 allografts exhibited vascularization at least equal to that induced by the original sutures, as well as a significant amount of corneal haze and edema. Grade 3 allografts exhibited corneal vascularization over one half to two thirds of the graft and were markedly hazy and thickened. Grade 4 allografts became completely vascularized, opaque, and edematous. Grade 4 grafts were considered rejected for the purposes of this study. A grade 1 condition was considered to be the beginning of an allograft immune reaction. The mean survival time was defined as the mean number of days required for all grafts in a group to reach grade 4 rejection.

To study prevention of graft reactions with cyclosporine in collagen shields or olive oil, 20 rabbits with previously vascularized corneas underwent penetrating keratoplasty (Group I). Treatment was begun immediately with cyclosporine in collagen shields or cyclosporine in olive oil. Shields were applied to ten of the grafts every five days for the first 25 days and then every 10 days until day 65. The grafts were observed every other day until day 120. Similarly, ten rabbits having undergone penetrating keratoplasties were treated with cyclosporine in olive oil (10 mg/ml) three times a day for the first 25 days and three times a day every ten days until day 65. Thereafter, the grafts were observed every other day for a total of 120 days.

To study reversal of graft reactions with cyclosporine in collagen shields or olive oil, 26 penetrating keratoplasties were performed into vascularized recipient graft beds (Group II). Two groups of ten animals each and two groups of three animals each bearing a corneal allograft in one eye were established. All grafts were observed on a daily basis by slit-lamp biomicroscopy. The day a graft exhibited evidence of a grade 1 corneal allograft reaction, treatment was begun. Ten allografts were treated three times a day for 60 days with cyclosporine in olive oil, and three with olive oil alone. Ten allografts were treated with cyclosporine in collagen shields and three with collagen shields alone every five days for 60 days. Throughout the treatment period (60 days) and the total observation period (120 days), the allografts were observed and the grade of the corneal allograft reaction recorded as described.

The Wilcoxon two-sample test was performed on the data obtained in both study groups. *T*-tests were performed to determine if statistically significant differences existed between various treatment groups.

Results

Allografts in vascularized graft beds demonstrated signs of immune attack soon after penetrating keratoplasty. All of the 17 grafts

TABLE 1

CORNEAL ALLOGRAFT IMMUNE REACTIONS IN VASCULARIZED AND NORMAL CORNEAS

NO. OF EYES	CONDITION OF RECIPIENT GRAFT SITE	TIME (DAYS) TO APPEARANCE OF GRADE 1 GRAFT REACTION	SURVIVAL TIME (DAYS)
17	Vascularized	11, 12, 13 (2)*, 14 (4), 15 (2), 16, 17, 22, 28 (2), 40, 43	19.3 ± 9.7†
8	Normal (not vascularized	17, 25, 58, >120 (5)	87.5 ± 46.3
5	Autografted	All surviving at 120 days	120 ± 0.0

*Numbers in parentheses indicate number of grafts for day indicated.

†Mean ± S.D. of the mean.

TABLE 2

EFFECT OF CYCLOSPORINE-CONTAINING COLLAGEN SHIELDS ON CORNEAL ALLOGRAFT SURVIVAL (IMMEDIATE TREATMENT)

TREATMENT	TOTAL NO. OF GRAFTS	NO. OF GRAFTS REJECTED	NO. (%) OF GRAFTS SURVIVING TO END POINT (120 DAYS)
Cyclosporine in collagen shields	10	1*	9 (90)
Cyclosporine in olive oil	10	8†	2 (20)

*Scored as grade 4 (rejected) on day 120.

†Scored as grade 4 (rejected) on days 27, 30, 36, 44, 46, 61, 65, and 87.

reached stage 4 rejection by 43 days after surgery; the mean survival time for the group was 19 days. Grafts in normal, unvascularized eyes survived longer. Five of the eight penetrating keratoplasty grafts and all of the autografts in the normal eyes survived the 120-day observation period (Table 1); the mean survival time for the penetrating keratoplasty grafts in normal eyes was 87.5 days. These results indicated that this high-risk graft model is appropriate for testing the effect of cyclosporine on graft survival.

In group I, of the 20 grafts treated beginning at the time of surgery, nine of the ten receiving cyclosporine in collagen shields but only two of the ten receiving cyclosporine in olive oil drops survived for the 120-day observation period (Table 2). The mean (± S.D.) survival time of allografts treated with cyclosporine in olive oil (63.6 days ± 34.7 days) was significantly less than that of the allografts treated with cyclosporine in collagen shields (119.9 days ± 0.32 days) ($P < .005$).

In group II, corneal allografts treated with cyclosporine in collagen shields survived longest. Clinically, in terms of the intensity of the graft reaction and rapidity of rejection, the immune response in these eyes during the treatment period appeared to be less severe, compared to the response in eyes receiving the drug in olive oil drops. The mean (± S.D.) survival time of the allografts treated with cyclosporine in collagen shields (100.8 days ± 31.75 days) was significantly greater ($P < .02$) than that of the allografts treated with cyclosporine in olive oil (41.7 days ± 37.6 days) (Table 3). Grafts treated with collagen shields or olive oil drops alone did not survive (Table 3).

A correlation between the intensity of the allograft reaction and the intensity of the T-lymphocyte infiltrate and class II$^+$ cells in the graft was noted in all treatment groups. The more intensely vascularized, opaque, and edematous the graft, the more pronounced was the infiltrate of T lymphocytes and class II$^+$ antigen–presenting cells. Generally, the allografts treated with cyclosporine in collagen shields exhibited less intense allograft reactions, had a less intense T-lymphocyte infiltrate, and contained fewer class II$^+$ cells, although we were unable to obtain statistically reliable cell counts.

At least five cryostat sections from all four

TABLE 3

EFFECT OF CYCLOSPORINE-CONTAINING COLLAGEN SHIELDS ON CORNEAL ALLOGRAFT SURVIVAL (DELAYED TREATMENT)*

TREATMENT	TOTAL NO. OF GRAFTS	NO. OF GRAFTS REJECTED	NO. (%) OF GRAFTS SURVIVING TO END POINT (120 DAYS)
Cyclosporine in collagen shields	10	3†	7 (70)
Cyclosporine in olive oil	7	6‡	1 (14)
Collagen shields alone	3	3	0 (0)
Olive oil alone	3	3	0 (0)

*Treatment began with first grade 1 reaction.

†Scored as grade 4 (rejected) on days 43, 52, and 73.

‡Scored as grade 4 (rejected) on days 13, 14, 22, 28, 40, and 55.

quadrants of each graft subjected to immunohistochemical staining were evaluated microscopically. Despite this microscopic analysis, it was not possible to obtain statistically significant estimates of the T-lymphocyte infiltrate and number of class II^+ cells in the various grafts examined. This difficulty was thought to be attributable to the uneven distribution of infiltrating mononuclear cells.

Discussion

The results of this investigation demonstrate that the collagen shield is an effective delivery system for the immunosuppressive drug, cyclosporine. These results indicate that cyclosporine delivered in this way can reverse corneal allograft rejection in its initial stages and ensure the long-term survival of corneal allografts.

Kaswan[7] reported that tritiated cyclosporine applied in olive oil drops entered the cornea in significant amounts and could also be found in the anterior chamber in small but measurable quantities. The amount and time course of the drug half-life in the cornea suggested that cyclosporine in olive oil resulted in peak drug levels shortly after delivery and that the drug dissipated rapidly. Mosteller and associates[8] found that a single application of cyclosporine dissolved in petrolatum ointment yielded cyclosporine in the cornea eight hours after application, but the drug was largely gone by 24 hours; no drug was found in the aqueous humor. Recently, Newton, Gebhardt, and Kaufman[9] reported that cyclosporine delivered in the penetration enhancer, Azone, retarded the immune graft reaction process. Relatively low concentrations of cyclosporine, however, were found in the corneas of the chronically treated eyes, and no drug was found in the aqueous humor or in the blood.

In other studies, Reidy, Gebhardt, and Kaufman[3] found that collagen shields containing cyclosporine consistently delivered high concentrations of the drug to the cornea and significant concentrations of the drug to the anterior chamber. This delivery system resulted in high drug concentration for up to eight hours after the application of a single shield in both the cornea and the aqueous humor. By 24 hours after a single application of cyclosporine in a collagen shield, the drug concentration in the cornea and aqueous humor had returned to baseline levels. These results, combined with the results of this study, emphasize the potential of the collagen shield as a delivery system for water insoluble drugs.

We found that cyclosporine in collagen shields prevented corneal allograft immune reaction when applied immediately after penetrating keratoplasty. Additionally, we found that cyclosporine in this drug delivery system halted and reversed corneal allograft immune reactions when treatment was begun early in the initial phases of the reaction. Grafts exhibiting grade 1 immune graft reactions (mild corneal haze and peripheral vascularization of the graft) cleared and the vessels regressed. Most of these grafts survived for 120 days. These results support the effectiveness of the collagen shield as a drug delivery system for cyclosporine in the eye.

The results of this study suggest that cyclosporine, a drug that interferes with antigen-driven T-cell activation, when applied locally to the cornea, can both prevent the initiation of immune graft rejection and reverse a graft reaction in progress. The potent effect of a locally administered drug on T cells that are recruited at distant locations highlights the utility of the collagen shield as a delivery system for this drug. These results suggest that cyclosporine has a direct effect on cell-mediated immune graft rejection and that this drug might be effective as a topically applied nonsteroidal anti-inflammatory agent for treating other ocular conditions.

Other investigators have attempted to study the capacity of cyclosporine to prevent or reverse immune reactions.[10-13] Generally, there is a relationship between drug concentration, the maintenance of drug levels in the organism, and the capacity of cyclosporine to reverse an ongoing immune graft reaction.[10,14] Future investigations involving modified forms of the collagen shield and studies of the half-life of drugs, such as cyclosporine, at the ocular surface and in the anterior segment will further establish this system's usefulness for treating ocular immune reactions.

ACKNOWLEDGMENT

Katherine L. Knight, Ph.D., Stritch School of Medicine, Loyola University at Chicago, provided the monoclonal antibody specific for the rabbit class II histocompatibility antigen, clone 2C4.

References

1. Belin, M. W., Bouchard, C. S., Frantz, S., and Chmielinska, J.: Topical cyclosporine in high-risk corneal transplants. Ophthalmology 96:1144, 1989.

2. Hill, J. C.: The use of cyclosporine in high-risk keratoplasty. Am. J. Ophthalmol. 107:506, 1989.

3. Reidy, J. J., Gebhardt, B. M., and Kaufman, H. E.: The collagen shield. A new vehicle for delivery of cyclosporine A to the eye. Cornea, in press.

4. Hill, J. C., and Maske, R.: An animal model for corneal graft rejection in high-risk keratoplasty. Transplantation 46:26, 1988.

5. Jackson, S., Chused, T. M., Wilkinson, J. M., Leiserson, W. M., and Kindt, T. J.: Differentiation of antigens identify subpopulations of rabbit T and B lymphocytes. J. Exp. Med. 157:34, 1983.

6. Lobel, S. A., and Knight, K. L.: The role of rabbit Ia molecules in immune functions as determined with the use of an anti-Ia monoclonal antibody. Immunology 51:35, 1984.

7. Kaswan, R. L.: Intraocular penetration of topically applied cyclosporine. Transplant. Proc. 20:650, 1988.

8. Mosteller, M. W., Gebhardt, B. M., Hamilton, A. M., and Kaufman, H. E.: Penetration of topical cyclosporine into the rabbit cornea, aqueous humor, and serum. Arch. Ophthalmol. 103:101, 1985.

9. Newton, C., Gebhardt, B. M., and Kaufman, H. E.: Topically applied cyclosporine in Azone prolongs corneal allograft survival. Invest. Ophthalmol. Vis. Sci. 29:208, 1988.

10. Thomson, A. W., Whiting, P. H., and Simpson, J. G.: Cyclosporine. Immunology, toxicity and pharmacology in experimental animals. Agents Actions 15:306, 1984.

11. Cohen, D. J., Loertscher, R., Rubin, M. F., Tilney, N. L., Carpenter, C. B., and Strom, T. B.: Cyclosporine. A new immunosuppressive agent for organ transplantation. Ann. Intern. Med. 101:667, 1984.

12. Reis, G. A. D., and Shevach, E. M.: Effect of cyclosporin A on T cell function in vitro. The mechanism of suppression of T cell proliferation depends on the nature of the T cell stimulus as well as the differentiation state of the responding T cell. J. Immunol. 129:2360, 1982.

13. Schulak, J. A., and Engelstad, K.: Cyclosporine abrogation of second-set rejection. Dependence upon major histocompatibility complex disparity. J. Surg. Res. 38:400, 1985.

14. Meuleman, J., and Katz, P.: The immunologic effects, kinetics, and use of glucocorticosteroids. Med. Clin. North Am. 69:805, 1985.

A Systematic Approach to the Diagnosis and Treatment of Chronic Conjunctivitis

Peter A. Rapoza, M.D., Thomas C. Quinn, M.D., Arlo C. Terry, M.D., John D. Gottsch, M.D., Lou Ann Kiessling, M.D., and Hugh R. Taylor, M.D.

In 58 patients with chronic conjunctivitis of greater than two weeks' duration, examination included obtaining an ocular and general medical history and performing a complete ophthalmic examination of the external eye. Conjunctival smears were obtained for Gram and Giemsa staining, direct immunofluorescent monoclonal antibody staining for *Chlamydia trachomatis* and herpes simplex virus, and chlamydial culture. Cultures for bacteria and viruses were obtained in 33 patients. The cause of the chronic conjunctivitis based on clinical and laboratory criteria was established in 40 of 58 (69%) patients: chlamydia, 11 (19%); virus, eight (14%); irritant, six (10%); allergen, four (7%); contact lens, four (7%); bacteria, four (7%); acne rosacea, two (3%); and floppy eyelid syndrome, one (2%). In 18 of 58 (31%) patients, no specific cause was detected. We recommend a systematic approach in the investigation of chronic conjunctivitis. Direct immunofluorescent monoclonal antibody staining is an effective and rapid technique for detecting chronic chlamydial conjunctivitis.

ALTHOUGH CHRONIC CONJUNCTIVITIS is an infrequent threat to sight, it is a common source of frustration to both patient and ophthalmologist. Persistent ocular burning, conjunctival injection, and ocular discharge are uncomfortable and unattractive, and may interfere with a patient's daily activities and prevent the use of contact lenses. Patients with chronic conjunctivitis have often used many treatments without significant relief.

Chronic conjunctivitis has many causes, including allergy, bacteria, chlamydia, insect larvae, viruses, topical medications, sebaceous gland carcinoma, contact lenses and solutions, floppy eyelid syndrome, acne rosacea, assorted irritants, and others.

A variety of approaches to determine the causes of chronic conjunctivitis have been proposed. Treatment is available to eliminate or alleviate the symptoms and signs of most types of chronic conjunctivitis.

We prospectively evaluated a systematic approach to diagnose and treat chronic conjunctivitis in 58 patients referred to a clinic specifically established to investigate chronic conjunctivitis.

To further improve diagnostic accuracy in patients with chronic conjunctivitis, we also prospectively evaluated direct fluorescent monoclonal antibody staining of conjunctival smears for *Chlamydia trachomatis* and herpes simplex virus.

Patients and Methods

Fifty-eight patients were referred to a special chronic conjunctivitis clinic. Before referral, each patient had undergone an ophthalmic examination by the referring physician. This examination included measurement of visual acuity, slit-lamp biomicroscopy, tonometry, and ophthalmoscopy. Patients with conjunctivitis secondary to blepharitis, keratoconjunctivitis sicca, or chronic dacryocystitis were excluded.

Informed consent was obtained from all pa-

Accepted for publication Nov. 21, 1989.

From the Department of Ophthalmology, the University of Wisconsin-Madison, Madison, Wisconsin (Dr. Rapoza); the Dana Center for Preventive Ophthalmology (Drs. Kiessling and Taylor) and the Cornea Service (Drs. Terry, Gottsch, and Taylor), Wilmer Ophthalmological Institute, and the Department of Medicine (Dr. Quinn), Johns Hopkins University, Baltimore, Maryland; and the National Institutes of Health, Bethesda, Maryland (Dr. Quinn). This study was supported in part by grants EY03324 and EY01765 from the National Institutes of Health, Bethesda, Maryland, and by a grant from the Syva Company, Palo Alto, California.

Reprint requests to Peter A. Rapoza, M.D., Department of Ophthalmology, University of Wisconsin-Madison, F4/336 CSC, 600 Highland Ave., Madison, WI 53792.

tients or their guardians at the time of enrollment in the study. Criteria for entry were conjunctival injection or ocular discharge or both present for more than two weeks before examination that showed no sign of resolution.

A standardized questionnaire was completed for each patient to evaluate the following: demographic factors; medical history; exposure, occupational, and allergic histories; characteristics of the patients' ocular complaints; and previous diagnostic studies, diagnoses, and treatments of the disorder. A complete external ophthalmic examination of each eye included palpation for preauricular and submandibular lymph nodes, evaluation of external and adnexal tissues, slit-lamp biomicroscopy of the anterior segment of the eye, application of fluorescein and rose bengal to the ocular surface, measurement of tear breakup time, and Schirmer's test with anesthesia. Further examination was performed by the individual examiner as necessary.

After topical anesthesia (0.5% proparacaine hydrochloride) was instilled in each eye, the inferior and superior palpebral conjunctiva of each eye was sampled with Dacron swabs (PurFybr, Inc., Munster, Indiana). The initial swab, prewetted with Schaedler's broth, was inoculated onto Thayer-Martin medium, chocolate agar, reduced blood agar, and Schaedler's broth. A second swab was rolled onto slides for direct immunofluorescent monoclonal antibody staining for *C. trachomatis* (MicroTrak, Syva Co., Palo Alto, California) and Giemsa staining (Diff-Quik, Harleco, Gibbstown, New Jersey), and placed into chlamydial transport media. A third swab was rolled onto slides for direct immunofluorescent monoclonal antibody staining to detect the presence of herpes simplex virus types I and II (Syva Co., Palo Alto, California) and Gram staining, and placed into viral transport media. Specimens from the initial 22 patients (Group 1) were processed for routine cytologic study, direct immunofluorescent monoclonal antibody staining for *C. trachomatis*, and chlamydial cultures. The remaining 36 patients (Group 2) underwent the complete battery of tests as detailed above.

Conjunctival smears for Gram and Giemsa staining were processed in the usual fashion. Stained slides were first evaluated by the examining physician and then reviewed by an ophthalmic pathologist who had no knowledge of the results of the other diagnostic studies. Aerobic and anaerobic bacterial cultures were processed in the usual fashion.

Slides for direct immunofluorescent monoclonal antibody staining were air-dried and then fixed with water-free acetone. Slides were refrigerated at 4 C and processed within 48 hours. A total of 30 μl of fluorescein-conjugated monoclonal antibody to *C. trachomatis* or herpes simplex virus types I and II was pipetted onto the appropriate specimen, which was kept within a humidified chamber at room temperature for 15 minutes, rinsed with water, and air-dried. Slides were read at $\times 640$ magnification under oil immersion by fluorescent microscopy. A specimen was considered positive for *C. trachomatis* if three or more typical elementary bodies were identified and positive for herpes simplex virus if one or more typical inclusions were noted. The examiner was masked to the results of the other diagnostic tests.

Chlamydial transport vials were immediately frozen to -70 C. Specimens were thawed within 48 hours and inoculated onto cycloheximide-treated McCoy cell monolayers in microtiter plates as previously described.[1] One set of duplicate wells was stained at two days (first passage), and another set passed at two days then stained at four days (second passage) with fluorescein-conjugated monoclonal antibody to *C. trachomatis*. Specimens were examined at $\times 400$ magnification and scored positive if one or more typical inclusion bodies were found.

Viral cultures were inoculated within 30 minutes of specimen collection onto human embryonic kidney cells and human diploid embryonic lung fibroblasts. Cultures were processed in the standard fashion.

Preliminary diagnosis and treatment were based on the assessment at the patient's initial examination, which included history, physical findings, and interpretation of routine cytologic smears. Subsequently, diagnosis and treatment were amended if the results of microbiologic identification assays indicated an inappropriate initial diagnosis or therapy.

Patients were contacted two to four days after the initial visit to communicate the results of diagnostic tests, assess response to treatment, and alter therapy if necessary. Return visits were performed one week after the cessation of antibiotic treatment or two to three weeks after the initiation of long-term therapeutic interventions.

Patients noted to have chlamydial conjunctivitis were instructed to refer their sexual partners to appropriate medical facilities for examination.

Results

Forty patients (69%) were placed in specific diagnostic categories (Table). Causes were not determined in 18 patients (31%).

Chlamydial conjunctivitis was diagnosed in 11 patients (19%). The efficacy of direct immunofluorescent monoclonal antibody staining in identifying chronic chlamydial conjunctivitis compared to the McCoy cell culture showed that direct immunofluorescent monoclonal antibody staining had a sensitivity of 80% and specificity of 98%. The positive and negative predictive values of the test were 89% and 96%, respectively.

Three discrepancies between the chlamydial assays were found. A positive direct immunofluorescent monoclonal antibody staining occurred in a 22-year-old man who had a six-week history of monocular redness and discharge. There was no lymphadenopathy, but a moderate follicular conjunctivitis was present. Routine cytologic studies demonstrated a mixed inflammatory cell infiltrate, but no bacteria or inclusion bodies. Cultures for bacteria, chlamydia, and viruses were negative. A two-week course of oral tetracycline resulted in complete resolution of the patient's disease. This patient was classified as having chlamydial conjunctivitis (Table).

A negative direct immunofluorescent monoclonal antibody staining was found in a 58-year-old woman who had acne rosacea and a three-month history of blepharoconjunctivitis. A McCoy cell culture was found to have one to ten inclusion bodies present per field at ×500 magnification at first passage. A Giemsa-stained conjunctival smear showed a moderate number of acute and chronic inflammatory cells. No organisms or inclusions were detected. Only *Staphylococcus epidermidis* was isolated from other cultures. A two-week course of oral tetracycline produced no change in the ocular signs or patient's symptoms. Continuous low-dose tetracycline resulted in significant improvement a few months later.

A negative direct immunofluorescent monoclonal antibody staining was found in a 36-year-old obese man who had a history of conjunctivitis of more than one year's duration. Physical findings included extremely loose upper eyelids with easily folded tarsal plates and papillary conjunctivitis. At first passage, the McCoy cells in the test well were destroyed whereas the control cells were normal. At second passage, one to ten inclusion bodies per field at ×500 magnification were detected. A moderate number of polymorphonuclear leukocytes were seen on the Giemsa-stained conjunctival smear. No inclusions or organisms were detected. *Staphylococcus epidermidis* was isolated by culture. No change in ocular status occurred after a two-week course of oral tetracycline. Ocular lubricants gave partial, but incomplete relief. A floppy eyelid syndrome was diagnosed, and the patient responded well to bilateral eyelid shortening procedures.

Two patients, despite negative direct immunofluorescent antibody staining and McCoy cell culture studies, were diagnosed as having chlamydial conjunctivitis on the basis of clinical examination. The first patient was a 22-year-old woman who had an eight-month history of bilateral ocular and vaginal discharge. Examination showed small, but palpable preauricular nodes and follicular conjunctivitis. A mixed inflammatory reaction with a predominance of lymphocytes was present on routine cytologic staining. Cultures for bacteria, chlamydia, and viruses were negative. The second patient was a 27-year-old woman who had a six-week history of bilateral ocular burning and discharge associated with preauricular lymphadenopathy and conjunctival follicles. A mixed inflammatory cell infiltrate was present on a routine conjunctival smear. The cultures showed no growth of organisms. Both patients responded with complete resolution of their conjunctivitis after a two-week course of oral tetracycline.

Although all Giemsa-stained conjunctival smears from patients in whom chlamydial conjunctivitis was diagnosed demonstrated mixed

TABLE
CLASSIFICATION OF CHRONIC CONJUNCTIVITIS BY CAUSE

CAUSE	GROUP 1 NO.	GROUP 1 %	GROUP 2 NO.	GROUP 2 %	TOTAL NO.	TOTAL %
Chlamydia species	7	32	4	11	11	19
Virus	3	14	5	14	8	14
Irritant	0	0	6	17	6	10
Allergy	1	4	3	8	4	7
Bacteria	0	0	4	11	4	7
Contact lens	0	0	4	11	4	7
Acne rosacea	0	0	2	6	2	3
Floppy eyelids	0	0	1	3	1	2
Unknown	11	50	7	19	18	31

inflammatory cell infiltrates, in no patients were basophilic intracytoplasmic inclusion bodies detected.

No viruses were isolated in culture or detected by direct immunofluorescent monoclonal antibody staining for herpes simplex virus. This includes specimens from eight patients in whom chronic adenoviral conjunctivitis was diagnosed clinically.

Of six cases of irritant conjunctivitis, five were associated with eye cosmetics and one with a thread-like foreign body. All cases resolved with removal of the inciting agents.

Cromolyn sodium was effective in treating three of the four cases of allergic conjunctivitis. Patients experienced a decrease or alleviation of their symptoms, and the conjunctiva was less inflamed in all patients. The fourth patient required the application of fluorometholone twice daily during the time she was completing a research project that required exposure to the identified allergen, rat dander.

Of four cases of chronic bacterial conjunctivitis, two were caused by *Staphylococcus aureus* and two by *S. epidermidis*. All resolved after a one-week course of topical antibiotic.

Three of the four cases of contact lens–associated conjunctivitis resolved after discontinuing the use of contact lens solutions containing thimerosal. The fourth patient was able to tolerate contact lenses with the use of topical cromolyn sodium. Giant papillary conjunctivitis was not present in any of the four patients.

In 18 patients (31%), a specific cause for chronic conjunctivitis could not be identified. This subset was composed of 11 of the 22 patients (50%) from Group 1 and seven of the 36 patients (19%) from Group 2.

Discussion

Chronic conjunctivitis is a relatively common ocular disorder that often defies clinical classification. Despite our efforts to use a systematic diagnostic approach, no causes could be established in 18 (31%) patients with chronic conjunctivitis. Dividing patients into those examined with a partial test battery (Group 1) and those in whom more complete testing was performed (Group 2), 11 of the former (50%), but only seven of the latter (19%) did not receive a specific diagnosis. Bacterial cultures assisted in establishing the diagnosis in patients with more extensive testing, but could not assist in the detection of irritants or the cause in contact lens–associated cases.

Our experience is similar to that of Thygeson and Kimura[2] in their classic study of chronic conjunctivitis. Unfortunately, one cannot know what percentage of their 907 patients composed "an important number of cases that resisted all attempts at clinical or etiologic differentiation."

The recent availability of improved microbiologic culture and identification techniques has led to an increase in diagnostic accuracy. The application of direct immunofluorescent monoclonal antibody staining to the identification of chlamydial conjunctivitis has been successful in neonates.[3,4] In comparison to McCoy cell chlamydial culture, direct immunofluorescent monoclonal antibody staining resulted in sensitivity of 100%, specificity of 94%, and positive and negative predictive values of 94% and 100%, respectively. Other investigators have reported a high sensitivity of direct immunofluorescent monoclonal antibody staining in diagnosing chlamydial conjunctivitis in adults, but one group noted the occurrence of false-positive tests compared to culture.[5]

Although we found Giemsa staining of conjunctival smears to be valuable in assessing the cytologic character of patients' inflammatory response, we were unable to detect chlamydial inclusion bodies on any Giemsa-stained smear. Other investigators report limited success. In one series, 387 adults with the clinical diagnosis of chlamydial conjunctivitis were noted to demonstrate typical intracytoplasmic inclusions on only 8% of Giemsa-stained conjunctival smears.[6] This series contained patients with acute and chronic conjunctivitis. In our experience, inclusions can be more readily demonstrated in acute than in chronic chlamydial infections.[3] Of 43 neonates with culture-proven chlamydial conjunctivitis, inclusion bodies were present on 18 smears (42%).

McCoy cell culture has been regarded as standard in the laboratory-confirmed diagnosis of chlamydial conjunctivitis. Despite the general acceptance of the culture technique, most clinicians recognize patients whom they believe to have chlamydial conjunctivitis despite a negative chlamydial culture.[3] Therefore, because of the imperfect reference standard of the McCoy cell culture, we cannot expect either the McCoy cell culture or direct immunofluorescent monoclonal antibody staining to diagnose accurately all cases of chlamydial conjunctivitis and may have to rely on therapeutic trials of

tetracycline or similar antibiotics in selected patients.

We recommend that all patients with chronic conjunctivitis undergo a systematic examination including history of systemic diseases, medications, and exposures associated with conjunctivitis; examination for the detection of ocular lymphadenopathy, eyelid abnormalities, presence of foreign bodies or irritants, characteristics of conjunctival reaction and discharge, adequacy of tearing, and presence of keratopathy; Gram and Giemsa staining of conjunctival smears; aerobic bacterial culture; and direct fluorescent monoclonal antibody staining of conjunctival smears or McCoy cell culture for C. *trachomatis*. We do not recommend a routine viral culture because of its failure to detect organisms in chronic conjunctivitis. If the cause of chronic conjunctivitis is not identified by the above methods, conjunctival biopsy may be useful for detecting other potentially treatable causes, including malignancy or ocular pemphigoid. We did not evaluate the role of biopsy in this series.

ACKNOWLEDGMENT

Supplies for direct immunofluorescent monoclonal antibody staining were provided by Syva Company.

References

1. Yoder, B. L., Stamm, W. E., Koester, C. M., and Alexander, E. R.: A microtest procedure for isolation of *Chlamydia trachomatis*. J. Clin. Microbiol. 13:1, 1981.
2. Thygeson, P., and Kimura, S. J.: Chronic conjunctivitis. Trans. Am. Acad. Ophthalmol. Otolaryngol. 67:494, 1963.
3. Rapoza, P. A., Quinn, T. C., Kiessling, L. A., Green, W. R., and Taylor, H. R.: Assessment of neonatal conjunctivitis with a direct immunofluorescent monoclonal antibody stain for *Chlamydia*. JAMA 255:3369, 1986.
4. Bell, T. A., Kuo, C. C., Stamm, W. E., Tam, M. R., Stephens, R. S., Holmes, K. K., and Grayston, J. T.: Direct fluorescent monoclonal antibody stain for rapid detection of infant *Chlamydia trachomatis* infections. Pediatrics 74:224, 1984.
5. Ugland, D. N., Jones, D. B., Wilhelmus, K. R., and Osato, M. S.: Diagnosis of adult chlamydial conjunctivitis by use of fluorescein-conjugated monoclonal antibody. Invest. Ophthalmol. Vis. Sci. 26(suppl.):272, 1985.
6. Wilhelmus, K. R., Robinson, N. M., Tredici, L. L., and Jones, D. B.: Conjunctival cytology of adult chlamydial conjunctivitis. Arch. Ophthalmol. 104:691, 1986.

Penetrating Keratoplasty for Keratoconus in Down's Syndrome

Jonathan M. Frantz, M.D., Michael S. Insler, M.D., Michael Hagenah, M.D., Marguerite B. McDonald, M.D., and Herbert E. Kaufman, M.D.

Five patients with Down's syndrome underwent penetrating keratoplasty for keratoconus. In three patients, the indication for surgery was acute corneal hydrops, which had not resolved in the three months before surgery. The other two patients had corneal scars. Two patients had combined penetrating keratoplasty, cataract extraction, and intraocular lens insertion. Four of the five patients maintained clear grafts at their most recent follow-up examination. Two of the five patients had one or more graft reaction episodes; one graft was lost. Good results can be obtained in penetrating keratoplasty for keratoconus in patients with Down's syndrome who do not demonstrate a tendency toward excessive eye rubbing and for whom a single observant caretaker can be relied on to provide consistent postoperative care.

THE OPHTHALMIC MANIFESTATIONS of Down's syndrome include mongoloid slant to the palpebral fissures, epicanthal folds, blepharoconjunctivitis, keratoconus, diffuse iris hypoplasia, Brushfield spots, lens opacities, strabismus, nystagmus, and ectropion.[1-6] The incidence of keratoconus in Down's syndrome has been estimated to be 6%.[1,3] Acute corneal hydrops is thought to be much more common in patients with Down's syndrome and keratoconus than in patients with keratoconus alone.[1,3-6] Cullen[6] studied 143 patients with Down's syndrome and found that 5% of these patients were blind in both eyes. Most of these patients became blind as a result of acute corneal hydrops or as a complication of cataract surgery. The restoration of functional vision in these patients deserves attention and treatment.[1]

In Cullen's study,[6] patients with Down's syndrome demonstrated numerous complications after cataract surgery; Cullen concluded that there was a poor prognosis for intraocular surgery in these patients. Generally, it has been assumed that the prognosis for penetrating keratoplasty is also poor in patients with Down's syndrome. This assumption is based on the inability of patients with Down's syndrome to report graft reactions or infections, their tendency to traumatize themselves or be traumatized by others, and their increased susceptibility to infections.[1,5]

Keratoconus is frequently found in patients with Down's syndrome, and occasionally these patients require penetrating keratoplasty for visual rehabilitation. In this study, we reviewed the records of all patients with Down's syndrome who underwent penetrating keratoplasty for keratoconus at our institution to determine graft survival and, when possible, visual results.

Accepted for publication Oct. 27, 1989.

From the LSU Eye Center, Louisiana State University Medical Center School of Medicine, New Orleans, Louisiana. This study was supported in part by U.S. Public Health Service grants EY02580 and EY02377 (Dr. Kaufman), EY07608 (Dr. Insler), and EY06094 (Dr. Frantz) from the National Eye Institute, National Institutes of Health, Bethesda, Maryland.

Reprint requests to Michael S. Insler, M.D., LSU Eye Center, 2020 Gravier St., Suite B, New Orleans, LA 70112-2234.

Patients and Methods

Between July 1, 1981, and July 1, 1987, six patients with Down's syndrome underwent penetrating keratoplasty for keratoconus at the LSU Eye Center. For patients with less than 12 months' follow-up, or who had not been seen at the LSU Eye Center in the last year, recent follow-up information was obtained from the

local ophthalmologist. One patient with three months' follow-up was excluded.

All five patients were men, ranging in age from 19 to 46 years. Three of the five patients underwent penetrating keratoplasty for acute corneal hydrops, which had not resolved in the three months before surgery. The remaining two patients underwent penetrating keratoplasty for central corneal scars, which were thought to be a result of previous episodes of acute corneal hydrops. Two of the patients had dense cataracts and underwent extracapsular cataract extraction and posterior chamber intraocular lens insertion at the time of penetrating keratoplasty. The average follow-up was 39 months (range, 14 to 64 months).

The technique for penetrating keratoplasty has been described.[7] In three of the patients, an 8-mm donor button was sutured into a 7.5-mm recipient trephined bed after cautery was applied to the corneal apex to shrink the cone. One patient (Patient 3) had a 7.75-mm donor button sutured into a 7.0-mm recipient trephined bed without cautery, and one patient (Patient 1) had an 8.0-mm donor button sutured into an 8.0-mm recipient trephined bed without cautery. Two of the five patients (Patients 1 and 4) underwent extracapsular cataract extraction with posterior chamber intraocular lens insertion at the time of penetrating keratoplasty. In three of the five patients, a double running 16-bite 10-0 nylon suture and a running 16-bite 11-0 nylon suture were used to close the corneal wound. In two of the patients (Patients 2 and 4), 16 interrupted 10-0 nylon sutures were placed followed by a running 11-0 nylon suture.

Results

Of the five patients with Down's syndrome who underwent penetrating keratoplasty for keratoconus (Table), four retained clear grafts at their most recent follow-up examination. Two of the five patients experienced one or more graft reaction episodes. One patient (Patient 1) had multiple graft reaction episodes, necessitating a total of three penetrating keratoplasties, each of which failed. In June 1986, the patient underwent a conjunctival flap procedure with a resulting visual acuity of hand motions. The other patient (Patient 4) had three graft reaction episodes, all of which were treated successfully. Each episode, however, required examination under anesthesia and a subtenon injection of corticosteroids. Postoperatively, this patient developed increased intraocular pressure, which was controlled by medications. Only one of the remaining four patients (Patient 2) with successful grafts was able to cooperate with visual acuity testing; visual acuity after surgery in this patient was 20/40.

Discussion

The graft clarity results in this study are not as good as those reported in previous studies of patients undergoing penetrating keratoplasty for keratoconus. In this study, four of five patients had clear grafts at their most recent follow-up examinations. Paglen and associates[8] reported 90% (292 of 326 eyes) clear grafts for keratoconus with a minimum follow-up of five years. Others have reported up to 98% (53 of 54 eyes[9] and 80 of 82 eyes[10]) with clear grafts after penetrating keratoplasty for keratoconus.

The small number of patients in this study may account for this discrepancy. The inability of Patient 1 to report symptoms of early graft rejection episodes led to repeated graft failures. This patient was living in a large institution for the severely retarded, and the various personnel who observed and treated his eye may have had difficulty detecting the early signs of graft rejection, which was an important factor in the unsuccessful outcome. In Patient 4, three graft reaction episodes were treated successfully. This patient lived with his parents, and daily observation and treatment of the operated on eye by the same family member led to early recognition and successful treatment of the graft reaction episodes. The 40% incidence (two of five) of graft rejection episodes in our patients is higher than the 6% (three of 50)[11] to 37.7% (20 of 53 eyes)[12] reported in larger series of nonretarded patients undergoing penetrating keratoplasty. It is not clear whether the high incidence is attributable to the small number of patients in this study, self-traumatization, noncompliance with medication, or other reasons. Further studies with larger numbers of Down's syndrome patients may clarify this issue.

None of the five patients developed wound separations. Binder and associates[13] reported a

TABLE
PATIENT DATA

PATIENT NO., SEX, AGE (YRS), EYE	DATE OF SURGERY	REASON FOR SURGERY	SURGERY	LENGTH OF FOLLOW-UP (MOS)	RESULTS	COMMENT
1, M, 19, L.E.	6/4/81	Acute hydrops, cataract	Penetrating keratoplasty (8.0-mm graft, 8.0-mm bed), extracapsular cataract extraction, posterior chamber intraocular lens; 10-0 and 11-0 nylon double running sutures, cautery	64	Three failed grafts caused by graft rejection, conjunctival flap 6/86, visual acuity of hand motions	Right eye—epikeratophakia, visual acuity of 20/80
2, M, 20, R.E.	1/19/84	Acute hydrops	Penetrating keratoplasty (8.0-mm graft, 7.5-mm bed); 16 interrupted 10-0 nylon sutures, 11-0 nylon running suture, cautery	36	Clear graft, visual acuity of 20/40	Left eye—epikeratophakia, visual acuity of 20/50
3, M, 46, R.E.	3/14/84	Corneal scar	Penetrating keratoplasty (7.75-mm graft, 7.70-mm bed); 10-0 and 11-0 nylon double running sutures	53	Clear graft, visual acuity not obtainable	—
4, M, 41, L.E.	5/6/86	Corneal scar, cataract	Penetrating keratoplasty (8.0-mm graft, 7.5-mm bed), extracapsular cataract extraction, posterior chamber intraocular lens; 16 interrupted 10-0 nylon sutures, 11-0 nylon running suture	26	Clear graft, visual acuity not obtainable	Three episodes of graft reaction treated successfully, postoperative glaucoma controlled on medication
5, M, 28, R.E.	10/27/87	Acute hydrops, involving entire cornea	Penetrating keratoplasty (8.0-mm graft, 7.5-mm bed); 10-0 and 11-0 nylon double running sutures, cautery	14	Clear graft, visual acuity not obtainable	—

5.7% incidence (21 of 369) of wound separations when either interrupted or running sutures were used. It is important to document the integrity of the wound at the completion of the penetrating keratoplasty in Down's syndrome patients because it is impossible for them to report the symptoms of wound separation or leak. None of our five patients demonstrated a propensity for eye rubbing or self traumatization. It is possible that eye rubbing or trauma might have led to wound leaks, separations, and a higher incidence of graft failure.

Most of the patients in this study were so severely retarded that accurate measurement of visual acuity was impeded. Nonetheless, those patients with clear grafts demonstrated improvement in behavioral and social interaction, which suggests a functional improvement in visual acuity.

There are few reported studies of penetrating keratoplasty for keratoconus in patients with Down's syndrome. Results similar to ours were reported by Slusher, Laibson, and Mulberger.[4] In a study of patients with Down's syndrome who underwent penetrating keratoplasty for keratoconus, they described five eyes of four patients, four of which had clear grafts at their most recent follow-up examination. Average follow-up in these patients was not described. One eye underwent three penetrating keratoplasties, all of which were unsuccessful.

After penetrating keratoplasty, two of five

patients in our study (Patients 1 and 2) underwent epikeratophakia for keratoconus in the contralateral eye, resulting in visual acuities of 20/80 and 20/50, respectively. In patients with keratoconus without central corneal scarring, and in whom mental retardation precludes successful contact lens wear, epikeratophakia remains an alternative to penetrating keratoplasty. The results of epikeratophakia for keratoconus have been good.[14-20] Epikeratophakia enables patients to avoid the risks of penetrating keratoplasty, including graft rejection, endophthalmitis, and wound leak, and does not require prolonged corticosteroid therapy, which might cause a cataract.[21] The Food and Drug Administration advisory panel has recommended approval of epikeratophakia for keratoconus in patients who have a poor prognosis for penetrating keratoplasty for various reasons, including numerous graft reactions in the fellow eye and severe mental retardation. Three of our five patients underwent penetrating keratoplasty for acute corneal hydrops and would have had to undergo penetrating keratoplasty for visual rehabilitation under any circumstances. The other two patients had central and paracentral scars, which may or may not have been treatable with epikeratophakia combined with reefing sutures[22] to move the scars away from the visual axis.

Ophthalmologists encounter many problems in the treatment of patients with keratoconus and Down's syndrome. Poor vision in these patients exacerbates feelings of isolation and results in poor social and behavioral interaction. Contact lens correction is complicated by difficulty in examining and fitting these patients and their inability to care for the lenses or report infections. In patients with poor vision because of keratoconus, we recommend epikeratophakia for those who do not have central or paracentral corneal scars. In those patients with corneal scarring within 1 mm of the visual axis or in patients with acute hydrops that does not clear within three months, we recommend penetrating keratoplasty. We have used reefing sutures[22] of 9-0 or 10-0 nylon placed in the host cornea to move paracentral scars away from the visual axis at the time of epikeratophakia. This technique, however, is best reserved for severely retarded patients with multiple caretakers or patients who demonstrate excessive eye rubbing or self traumatization, behaviors which make these patients poor candidates for penetrating keratoplasty.

The results of this study indicate that the outcome of penetrating keratoplasty can be satisfactory in patients with Down's syndrome, especially in those patients who do not exhibit a tendency toward eye rubbing, self traumatization, and for whom a single caretaker can aid in the observation and treatment of the eye postoperatively.

References

1. Skeller, E., and Oster, J.: Eye symptoms in mongolism. Acta Ophthalmol 29:149, 1952.
2. Eissler, R., and Longenecker, P.: The common eye findings in mongolism. Am. J. Ophthalmol. 54:398, 1969.
3. Cullen, J. F., and Butler, H. G.: Mongolism (Down's syndrome) and keratoconus. Br. J. Ophthalmol. 47:321, 1963.
4. Slusher, M. M., Laibson, P. R., and Mulberger, R. D.: Acute keratoconus in Down's syndrome. Am. J. Ophthalmol. 66:1137, 1968.
5. Walsh, S. Z.: Keratoconus and blindness in 469 institutionalized subjects with Down's syndrome and other causes of mental retardation. J. Ment. Defic. Res. 25:243, 1981.
6. Cullen, J. F.: Blindness in mongolism (Down's syndrome). Br. J. Ophthalmol. 47:331, 1963.
7. Olson, R. J.: Corneal transplantation techniques. In Kaufman, H. E., Barron, B. A., McDonald, M. B., and Waltman, S. R. (eds.): The Cornea. New York, Churchill Livingstone, 1988, pp. 743–785.
8. Paglen, P. G., Fine, M., Abbott, R. L., and Webster, R. G: The prognosis for keratoplasty in keratoconus. Ophthalmology 89:654, 1982.
9. Ehlers, N., and Olsen, T.: Long term results of corneal grafting in keratoconus. Acta Ophthalmol. 61:918, 1983.
10. Troutman, R. C., and Gaster, R. N.: Surgical advances and results of keratoconus. Am. J. Ophthalmol. 90:131, 1980.
11. Anseth, A.: Keratoplasty for keratoconus. A report of 50 operated eyes. Acta Ophthalmol. 45:684, 1967.
12. Chandler, J. W., and Kaufman, H. E.: Graft reactions after keratoplasty for keratoconus. Am. J. Ophthalmol. 77:543, 1974.
13. Binder, P. S., Abel, R., Polack, F. M., and Kaufman, H. E.: Keratoplasty wound separations. Am. J. Ophthalmol. 80:109, 1973.
14. Kaufman, H. E., and Werblin, T. P.: Epikeratophakia for the treatment of keratoconus. Am. J. Ophthalmol. 93:342, 1982.
15. McDonald, M. B., Koenig, S. B., Safir, A., and Kaufman, H. E.: On-lay lamellar keratoplasty for the treatment of keratoconus. Br. J. Ophthalmol. 67:615, 1983.

16. McDonald, M. B., Kaufman, H. E., Durrie, D. S., Keates, R. H., Sanders, D. R., and the other Medical Monitors of the Nationwide Epikeratophakia Study: Epikeratophakia for keratoconus. The nationwide study. Arch. Ophthalmol. 104:1294, 1986.

17. Lass, J. H., Stocker, E. G., Fritz, M. E., and Collie, D. M.: Epikeratoplasty. The surgical correction of aphakia, myopia, and keratoconus. Ophthalmology 94:912, 1987.

18. Steinert, R. F., and Wagoner, M. D.: Long-term comparison of epikeratoplasty and penetrating keratoplasty for keratoconus. Arch. Ophthalmol. 106:493, 1988.

19. Dietze, T. R., and Durrie, D. S.: Indications and treatment of keratoconus using epikeratophakia. Ophthalmology 95:236, 1988.

20. McDonald, M. B., Safir, A., Waring, G. O., Schlichtemeier, W. R., Kissling, G. E., and Kaufman, H. E.: A preliminary comparative study of epikeratophakia or penetrating keratoplasty for keratoconus. Am. J. Ophthalmol. 103:467, 1987.

21. Donshik, P. C., Cavanagh, H. D., Boruchoff, S. A., and Dohlman, C. H.: Posterior subcapsular cataracts induced by topical corticosteroids following keratoplasty for keratoconus. Ann. Ophthalmol. 13:29, 1981.

22. McDonald, M. B., and Kaufman, H. E.: Epikeratophakia for aphakia, myopia, and keratoconus. In Waltman, S. R., Keates, R. H., Hoyt, C. S., Fruch, B. R., Herschler, J., and Carroll, D. M. (eds.): Surgery of the Eye, vol. 1. New York, Churchill Livingstone, 1988, pp. 243–261.

OPHTHALMIC MINIATURE

This name has an aura around it, like an amulet, some charm that's survived from an unimaginably distant past. I lie in my single bed at night, with my eyes closed, and the name floats there behind my eyes, not quite within reach, shining in the dark.

Margaret Atwood, *The Handmaid's Tale*
Boston, Houghton Mifflin Company, 1986, p. 84

Retinal Detachment in Penetrating Keratoplasty Patients

Paul Sternberg, Jr., M.D., Travis A. Meredith, M.D., Michael A. Stewart, M.D., and Henry J. Kaplan, M.D.

We reviewed the records of 23 patients who had retinal detachment after penetrating keratoplasty. Seventeen retinas (74%) were reattached successfully. Of the six failures, four patients had hemorrhagic choroidal detachment at the time of keratoplasty. When these complex retinal detachments are subtracted, 17 of 19 patients (89%) had successful retinal reattachments. Of the 17 successes, only seven patients had visual acuity of 20/200 or better. Retinal detachments after penetrating keratoplasty can be repaired with a high rate of success, but visual results remain disappointing.

ADVANCED TECHNIQUES of microsurgery and modern eyebanking have made penetrating keratoplasty an increasingly successful surgical procedure for a variety of diseases causing corneal opacification. Even in the presence of a clear graft, visual results can be compromised by a variety of complications including glaucoma, cataract, cystoid macular edema, and retinal detachment.

Retinal detachment is a well-documented complication of cataract surgery, with detachment rates of 2% to 4%[1] reported with intracapsular extraction and 0.02% to 3.6%[2] with extracapsular extraction. Although retinal detachments in aphakic and pseudophakic eyes may have a larger number of associated retinal tears causing increased difficulty for surgical repair, reattachment rates greater than 90% have been reported consistently.[3]

Less is known about retinal detachments in penetrating keratoplasty patients. Two large reviews of penetrating keratoplasties have calculated retinal detachment rates in the same range as that after cataract surgery. These retinal detachments, however, were repaired successfully only 28.6% and 53.6% of the time.[4,5]

We reviewed the records of 23 patients who had retinal detachment after penetrating keratoplasty. We also evaluated the effect of retinal detachment and subsequent surgery on the survival of the corneal graft.

Material and Methods

We reviewed the surgical records of the Emory University Retina Service from 1980 to 1987 and identified 23 eyes of 23 patients with penetrating keratoplasties who underwent retinal reattachment surgery.

Outpatient and inpatient records were reviewed to identify the date of penetrating keratoplasty, indication for surgery, adjunctive procedures performed at the time of surgery (cataract extraction, intraocular lens placement, exchange or removal of intraocular lens, anterior vitrectomy, goniosynechiolysis), patient age, best postgraft visual acuity, and postkeratoplasty course, including graft clarity, intraocular lens status, cystoid macular edema, and intraocular pressure. Time between penetrating keratoplasty and retinal detachment was calculated.

The status of eyes with retinal detachment before repair was reviewed to determine visual acuity, corneal graft status, intraocular lens status, intraocular pressure, extent of retinal detachment, number of retinal breaks, and degree of proliferative vitreoretinopathy. Reports were reviewed to confirm presurgical retinal status, including the number of retinal breaks. The type of surgery performed was noted: retinal scleral exoplant, encircling exoplant, pars plana vitrectomy, silicone oil injection, or pneumatic retinopexy.

Accepted for publication Dec. 4, 1989.

From the Department of Ophthalmology, Emory University School of Medicine, Atlanta, Georgia. This study was supported by a departmental grant from Research to Prevent Blindness, Inc., and by departmental core grant P30 EY06360 from the National Institutes of Health.

Reprint requests to Paul Sternberg, Jr., M.D., Emory University School of Medicine, 1327 Clifton Rd. N.E., Atlanta, GA 30322.

All patients were followed up for a minimum of six months unless retinal surgery was deemed unsuccessful and additional surgery was not recommended. Follow-up data were obtained to determine visual acuity, corneal graft status, intraocular pressure, intraocular lens status, and retinal status.

Results

Retinal reattachment surgery was performed on 23 eyes of 23 patients who had undergone corneal transplantation previously.

In 12 eyes (52%), penetrating keratoplasty had been performed for bullous keratopathy (aphakic, eight eyes, and pseudophakic, four eyes). In four eyes, keratoplasty was performed for Fuchs' dystrophy. The remaining eyes had corneal surgery for a variety of reasons, including keratoconus, leukoma, and interstitial keratitis. The corneal graft was clear in 13 (57%) of the eyes at the time of diagnosis of the retinal detachment. In nine eyes (39%), the cornea had minimal-to-moderate haze or folds. The cornea was cloudy with a failed graft in only one eye.

All 23 eyes were either aphakic or pseudophakic at the time of retinal detachment. All but one of the eyes had undergone two or more anterior segment procedures before retinal detachment, with an average of 2.7 previous operations. Because many of the eyes had previous intracapsular cataract extraction, anterior vitrectomy had been performed at the time of penetrating keratoplasty in 18 (78%) of the eyes. All of these procedures were performed through an open sky approach (Table 1).

Eleven of the retinal detachments were diagnosed within six months of the corneal transplant. Six occurred between six and 24 months after the penetrating keratoplasty and six after 24 months. Of the 23 detachments, 19 involved the macula; 11 of these were total detachments. Proliferative vitreoretinopathy was present preoperatively in nine of the 23 eyes. In four eyes, hemorrhagic choroidal detachment occurred at the time of the preceding penetrating keratoplasty.

In 19 eyes, the initial operation was a scleral buckle. Scleral buckle with vitrectomy was attempted in three eyes and vitrectomy alone in one.

Of the 23 retinal detachments, anatomic reattachment was achieved in 17 (74%). Anatomic success was evaluated in relation to several

TABLE 1
PREOPERATIVE STATUS OF 23 EYES

STATUS OF EYE	TOTAL NO. OF EYES	NO OF RETINAS REATTACHED (%)
Visual acuity		
20/40	3	3 (100)
20/50 to 5/200	1	0 (0)
Counting fingers	7	6 (86)
Hand motions/light perception	12	7 (58)
Lens status		
Aphakic	18	12 (67)
Pseudophakic	5	5 (100)
Vitreous status		
Previous vitrectomy	18	12 (78)
No vitrectomy	5	5 (100)
Time between penetrating keratoplasty and retinal detachments		
6 mos	11	6 (54)
6 to 24 mos	6	6 (100)
24 mos	6	5 (83)

aspects of preoperative status (Table 2). Of the 11 total retinal detachments, seven were reattached (63%). Preoperative proliferative vitreoretinopathy was noted in nine of the 21 eyes; six of these retinas were attached successfully (54%). Of those patients without preoperative proliferative vitreoretinopathy, 11 of 14 retinas (79%) were successfully reattached. None of the four eyes with hemorrhagic choroidal detachment and retinal detachment were reattached. However, 17 of the 19 eyes (89%) without choroidal detachment had anatomic success.

In addition to the four eyes with preoperative hemorrhagic choroidal detachment, two other eyes were unsuccessfully treated; one had proliferative vitreoretinopathy before initial surgery. After failing with a scleral buckle, the patient refused reoperation with vitrectomy. In the sixth eye, vitrectomy with gas injection was chosen as the initial operation in an attempt to preserve a functional filtering bleb.

Of the 17 retinas successfully reattached, only seven had final visual acuity of 20/200 or better. Four additional eyes had visual acuity of between 20/300 and 5/200 (Table 3). Of the 16 eyes with visual acuity worse than 20/200, three eyes had opaque corneas, three had significant macular puckers, and two had severe glaucoma. In the other eight eyes, the poor

TABLE 2
CHARACTERISTICS OF RETINAL DETACHMENT IN 23 EYES

CHARACTERISTIC	NO. OF EYES	NO. OF RETINAS ATTACHED (%)
No. of quadrants		
1	3	3 (100)
2	6	5 (83)
3	3	2 (67)
4	11	7 (63)
Status of macula		
Involved	19	14 (72)
Spared	4	3 (75)
No. of breaks		
0	7	5 (71)
1	12	10 (83)
2	4	2 (50)
Grade of proliferative vitreoretinopathy*		
None	14	11 (79)
A or B	2	2 (100)
C-1	4	3 (75)
C-2	2	1 (50)
D-3	1	0 (0)

*Classification according to the Retina Society Terminology Committee.

vision was ascribed to macular damage caused by the duration of the retinal detachment. A total of 33 operations were performed to achieve retinal reattachment. Of the 17 eyes with anatomic reattachment, five required reoperation. Reoperation was unsuccessful in five additional eyes. Six of 11 retinal detachments (54%) occurring within six months of penetrating keratoplasty were successfully repaired, whereas 12 of 13 (92%) later-occurring detachments were successfully repaired.

The corneal graft remained clear in 14 of 23 eyes. Twelve of 17 anatomic successes had clear corneas; three required repeat keratoplasty. Two of six eyes failing retinal surgery maintained clear grafts. Complications included the following: glaucoma in five eyes, three of which required cyclotherapy; corneal graft opacification in six eyes, four of which required repeat penetrating keratoplasty; epiretinal membrane in three eyes, one of which required vitrectomy with membrane peeling; recurrent retinal detachment in ten eyes, four of which were reattached with additional surgery; and extruded exoplant in one eye. The 23 eyes underwent a total of 41 operations.

TABLE 3
FINAL VISUAL ACUITY IN 23 EYES

VISUAL ACUITY	NO. OF EYES	NO. OF RETINAS ATTACHED
20/40	3	3
20/50 to 20/200	4	4
20/300 to 5/200	4	4
Counting fingers	4	4
Hand motions	4	2
Light perception	3	0
No light perception	1	0

Discussion

Although retinal detachment is an uncommon complication of penetrating keratoplasty, previous reports have suggested that it is devastating. Of 14 retinal detachments following penetrating keratoplasty reported by Forstot and associates,[4] only four (29%) were reattached.[4] Musch and associates[5] described 28 eyes with detachments after corneal graft surgery, finding a reattachment rate of only 54% (15 eyes). Rosenthal, Sabates, and Insler[6] reported a series of only seven eyes, but all achieved anatomic reattachment.

In our series of 23 eyes, anatomic reattachment was achieved in 17 eyes (74%). Additionally, review of the six anatomic failures disclosed a hemorrhagic choroidal detachment at the time of the most recent keratoplasty in four eyes. Purcell and associates[7] reported that only two of 14 eyes with expulsive hemorrhage complicating penetrating keratoplasty regained light perception. Of three eyes reported by Lambrou, Meredith, and Kaplan[8] with expulsive hemorrhage after penetrating keratoplasty, one eye regained a visual acuity of counting fingers; the remaining two eyes had a visual acuity of no light perception. The authors state that repair of retinal detachment after choroidal hemorrhage may be complicated by forcible apposition of retinal tissue to the iris and pars plana, lending a tractional component to the ensuing retinal detachment.

When the four eyes that had hemorrhagic choroidal detachment at the time of the most

recent keratoplasty are subtracted from the 23 eyes studied, the rate of anatomic reattachment for retinal detachment after penetrating keratoplasty was 89% (17 of 19 eyes). This analysis indicates that anatomic success can be achieved in most retinal detachments following penetrating keratoplasty. Only seven of the 23 eyes (30%), however, achieved visual acuity of 20/200 or better. In the report of Musch and associates,[5] only five of 28 eyes (25%) achieved similar visual acuity.

Because of the patient's poor visual acuity after penetrating keratoplasty, there may be a delay in the diagnosis of retinal detachment; only four patients underwent examination before the detachment spread to involve the macula. Furthermore, more than half of the eyes had detachments involving three or more quadrants; ten eyes (43%) had total detachments.

Patients who undergo penetrating keratoplasty do not have good visual acuity for many months after surgery. If the fellow eye has excellent acuity, the patient is frequently accustomed to not using the transplanted eye and is thus asymptomatic at the time of the retinal detachment. Of the 23 eyes, only four (17%) had a preoperative visual acuity of 20/200 or better. The higher rate of reattachment in eyes identified more than six months after transplant may reflect the more rapid detection of the retinal detachment. At six months after transplantation, vision is often improved enough that the patient will notice the retinal detachment and return to their ophthalmologist for examination. The four patients with macular sparing detachments had their transplants several years before the retinal detachment and were symptomatic at the time of diagnosis. The delay in diagnosis in many of our patients is reflected in the 39% (nine of 23 eyes) incidence of advanced proliferative vitreoretinopathy. Of course, the high incidence of proliferative vitreoretinopathy may be related to the multiple previous procedures, with associated inflammation and vitreous manipulation.

Poor vision after retinal reattachment was caused by corneal opacification in three eyes, glaucoma in two eyes, and epiretinal membrane in two eyes. The cases of epiretinal membrane or macular pucker can be related to the retinal reattachment surgery. A certain degree of vision loss, however, is related to the status of the anterior segment. Most of the eyes had multiple operations before retinal detachment, often leading to peripheral anterior synechiae formation and secondary glaucoma. Additionally, many of the eyes underwent more than one previous keratoplasty. The surgical manipulation and postoperative inflammation accompanying retinal reattachment surgery threatens the integrity of the graft. For this reason, the surgeon may be reluctant to use air, gas, or silicone oil as adjunctive forms of treatment for these retinal detachments. These internal tamponade treatments play an increasingly critical role in successful vitreoretinal surgery, particularly in the presence of previous vitrectomy, as was the case in almost all of the eyes studied. These agents, however, have been reported to damage the cornea, leading to corneal decompensation.[9,10] Despite concerns about maintaining corneal graft clarity, 25% of the eyes with successful retinal surgery suffered some degree of subsequent opacification. Three of the 17 grafts failed. Forstot and associates[4] noted one graft failure of three reattached retinas; Rosenthal, Sabates, and Insler,[6] however, had only one graft failure out of seven eyes that underwent retinal detachment and penetrating keratoplasty.

Although previous reports have noted poor anatomic success in eyes with penetrating keratoplasty and retinal detachment, our study demonstrates that retinal reattachment can be achieved in 74% of patients. In addition to the nine eyes (39%) that had various degrees of proliferative vitreoretinopathy, three eyes (13%) failed because of the development of proliferative vitreoretinopathy, a rate which is considerably higher than that reported for other retinal detachments in aphakic eyes. This rate may be partially explained by the cumulative number of operations on these eyes, including anterior vitrectomy. This rate may also be explained by the likelihood of multiple retinal breaks; all of these eyes were aphakic and required substantial cryotherapy. More likely, the rate of 13% is explained by the preexisting, but unobserved, anterior proliferative vitreoretinopathy, which developed after expulsive choroidal hemorrhage in four eyes when the anterior vitreous was rolled toward the anterior pars plana and posterior iris.[11]

Obtaining good visual results with retinal detachments after penetrating keratoplasty is difficult. Good visual results require early diagnosis, which is aided by a ophthalmoscopic examination through a dilated pupil at the time of each cornea follow-up examination, particularly in the first six months when the patient's

poor visual acuity may preclude awareness of the condition.

References

1. Scheie, H. G., Morse, P. H., and Aminlari, A.: Incidence of retinal detachment following cataract extraction. Arch. Ophthalmol. 89:293, 1973.
2. Coonan, P., Fung, W. E., Webster, R. G., Allen, A. W., and Abbot, R. L.: The incidence of retinal detachment following extracapsular cataract extraction. A ten year study. Ophthalmology 92:1096, 1985.
3. Wilkinson, C. P.: Pseudophakic retinal detachments. Retina 5:1, 1985.
4. Forstot, S. L., Binder, P. S., Fitzgerald, C., and Kaufman, H. E.: The incidence of retinal detachment after penetrating keratoplasty. Am. J. Ophthalmol. 80:102, 1975.
5. Musch, D. C., Meyer, R. F., Sugar, A., and Vine, A. K.: Retinal detachment following penetrating keratoplasty. Arch. Ophthalmol. 104:1617, 1986.
6. Rosenthal, W. N., Sabates, M. A., and Insler, M. S.: The effects of retinal detachment repair on clear corneal grafts. Am. J. Ophthalmol. 101:164, 1986.
7. Purcell, J. J., Krachmer, J. H., Doughman, D. J., and Bourne, W. M.: Expulsive hemorrhage in penetrating keratoplasty. Ophthalmology 89:41, 1982.
8. Lambrou, F. H., Meredith, T. A., and Kaplan, H. J.: Secondary surgical management of expulsive choroidal hemorrhage. Arch. Ophthalmol. 105:1195, 1987.
9. Van Horn, D. L., Edelhauser, H. F., Aaberg, T. M., and Pederson, H. J.: In vivo effects of air and sulfur hexafluoride gas on rabbit corneal endothelium. Invest. Ophthalmol. 11:1028, 1972.
10. Sternberg, P., Hatchell, D. L., Foulks, G. N., and Landers, M. B.: The effect of silicone oil on the cornea. Arch. Ophthalmol. 103:90, 1985.
11. Lewis, H., and Aaberg, T. M.: Anterior proliferative vitreoretinopathy. Am. J. Ophthalmol. 105:277, 1988.

OPHTHALMIC MINIATURE

Rieux could follow the vicissitudes of the struggle only in his friend's eyes, now open and now shut; in the eyelids, now more closely welded to the eyeball, now distended; and in his gaze fixed on some object in the room or brought back to the doctor and his mother. And each time it met the doctor's gaze, with a great effort Tarrou smiled.

Albert Camus, *The Plague*, trans. by Stuart Gilbert
New York, Vintage Books, 1948, p. 265

Hemorheologic Abnormalities in Patients With Human Immunodeficiency Virus Infection and Ophthalmic Microvasculopathy

Robert E. Engstrom, Jr., M.D., Gary N. Holland, M.D., W. David Hardy, M.D., and Herbert J. Meiselman, Sc.D.

The severity of conjunctival microvascular changes and the presence of cotton-wool spots were compared to factors that may affect blood flow (hematocrit level, red cell aggregation, fibrinogen level, plasma viscosity, circulating immune complexes, and quantitative immunoglobulin levels) in 22 human immunodeficiency virus-infected individuals. The severity of conjunctival disease was associated with increased zeta sedimentation ratios (a measure of red cell aggregation) and fibrinogen levels. The presence of cotton-wool spots was also associated with higher fibrinogen levels. Plasma viscosity and quantitative IgG levels were above normal levels in most patients, although a relationship to disease severity was not established. Altered blood flow may contribute to vascular damage and ocular ischemic lesions in patients with human immunodeficiency virus infection.

MICROVASCULAR DISEASE is a frequent finding in patients with the acquired immunodeficiency syndrome (AIDS) and other disorders associated with human immunodeficiency virus infection. Cotton-wool spots, the most common ocular lesions in these patients, are believed to result from focal ischemia associated with microvasculopathy of the retina.[1,2] Other less common retinal vascular disorders include hemorrhages, microaneurysms, and microvascular abnormalities on fluorescein angiography.[1-3] These changes frequently occur around cotton-wool spots, suggesting that they may be related to common disease mechanisms.[3] Microvascular abnormalities also have been reported in the conjunctivae of patients with human immunodeficiency virus infection.[4]

Similar retinal lesions, including microaneurysms and cotton-wool spots, occur with diabetes mellitus, chronic myelogenous leukemia,[5,6] systemic lupus erythematosus,[7] and multiple myeloma.[8,9] Similar conjunctival vascular changes occur in sickle cell disease,[10-14] chronic myelogenous leukemia,[15] and ataxia-telangiectasia.[16,17]

Abnormal blood flow dynamics are believed to contribute to the development of microvascular changes in disorders other than AIDS.[18] Hemorheology (the study of deformation and flow properties of cellular and plasmatic components of blood) may provide some insight into the pathogenesis of human immunodeficiency virus–associated microvascular disease as well, and may provide a unifying explanation for the similarities between various unrelated disorders that involve microvascular lesions. To determine whether altered blood flow is associated with the microvasculopathy of human immunodeficiency virus infection, the severity of conjunctival microvascular changes and the presence of cotton-wool spots were compared to hemorheologic factors determined on blood from human immunodeficiency virus–infected patients.

Accepted for publication Oct. 4, 1989.

From the AIDS Unit of the UCLA Uveitis Center, the Jules Stein Eye Institute (Drs. Engstrom and Holland), the UCLA AIDS Center (Dr. Hardy), and the Departments of Ophthalmology (Drs. Engstrom and Holland) and Medicine (Dr. Hardy), UCLA School of Medicine, Los Angeles, and the Department of Physiology and Biophysics, University of Southern California School of Medicine, Los Angeles (Dr. Meiselman). This study was supported in part by a Research Manpower Award from Research to Prevent Blindness, New York, New York (Dr. Holland), and by National Institutes of Health Research Grant HL15722 (Dr. Meiselman). Dr. Holland is recipient of the Research to Prevent Blindness–James S. Adams Scholar Award.

Reprint requests to Gary N. Holland, M.D., Jules Stein Eye Institute, UCLA Medical Center, 10833 Le Conte Ave., Los Angeles, CA 90024-1771.

Material and Methods

Twenty-two white homosexual or bisexual men with antibodies to human immunodeficiency virus were included in this study. Patients were selected randomly, without regard to the presence of ocular signs or symptoms, from a medical clinic that provides care to individuals with AIDS and other human immunodeficiency virus–associated disorders. Human immunodeficiency virus infection was documented by enzyme-linked immunosorbent assay testing. No patient had other medical disorders known to cause conjunctival or retinal vascular disease.

Associations with possible confounding variables were investigated. Demographic and medical information obtained from each patient included age, interval since human immunodeficiency virus infection was diagnosed, stage of human immunodeficiency virus–related illness (asymptomatic infection, AIDS-related complex, or AIDS), history of *Pneumocystis carinii* pneumonia, and use of zidovudine (also known as azidothymidine or AZT). A diagnosis of AIDS was based on Centers for Disease Control criteria.[19] Patients who had clinical signs or symptoms attributable to human immunodeficiency virus infection, but who did not fulfill Centers for Disease Control criteria for the diagnosis of AIDS, were considered to have AIDS-related complex. A history of *P. carinii* pneumonia was considered because of reports suggesting a relationship between it and microvascular disease.[20] The use of zidovudine was considered because its use is associated with a decrease in the incidence of secondary opportunistic infections, which might affect circulating immune complex and immunoglobulin levels, and because of its bone marrow toxicity that can cause anemia and low hematocrit levels.[21] Patients entered the study after receiving informed consent under an institutional review board-approved protocol.

Biomicroscopic examination—Conjunctivae of both eyes in each patient were examined by biomicroscopy. Because all patients had some evidence of conjunctival microvasculopathy in both eyes, patients were given scores based on the severity of signs. Examinations were performed on all patients at an examination session that allowed comparison of conjunctival findings between patients and facilitated placement of patients into groups of relative severity.

Conjunctival microvascular disease was defined as the presence of blood-flow sludging and changes in vessel structure. Assessment of blood-flow sludging was based on the degree of granularity in the blood column, the speed of blood flow, and the location and size of vessels with a granular blood column. Assessment of changes in vessel structure was based on the presence, size, and location of dilated limbal capillaries, microaneurysms, isolated vascular fragments, and vessel segments of irregular caliber (Figure).

A grading of 1+ (mild) was given for blood-flow sludging if the granular blood column was observed primarily at the limbus and blood flow was rapid. A grading of 2+ (severe) was given if the granular blood column was observed in vessels far from the limbus or in deep vessels, and blood flow was slow.

A grading of 1+ (mild) was given for changes in vessel structure if no structural changes were observed or if the changes were limited to rare or isolated clusters in the perilimbal areas. A grading of 2+ (severe) was given if there were microaneurysms, isolated vascular fragments, and vessel segments of irregular caliber located throughout the bulbar conjunctiva.

Although a direct association between blood-flow sludging and changes in vessel structure has not been established, they appear to be correlated on clinical examination. Each patient, therefore, was also given a single conjunctival microvasculopathy score indicating disease severity.

Patients were given a conjunctival microvasculopathy score of "mild" if there were no structural changes or only a slight dilation of capillaries at the limbus in isolated areas; rare microaneurysms, vascular fragments, or vessel segments of irregular caliber; sludging visible primarily at the limbus; and rapid flow of the granular blood column.

Patients were given a conjunctival microvasculopathy score of "moderate" if there were dilated capillaries involving most of the limbus; isolated groups of microaneurysms, vascular fragments, and vessel segments of irregular caliber; sludging visible in vessels remote from the limbus; and slow blood flow.

Patients were given a conjunctival microvasculopathy score of "severe" if there were marked dilation of limbal capillaries throughout the circumference of the cornea; widespread microaneurysms, vascular fragments, and vessel segments of irregular caliber involving multiple clock hours of the limbus and areas of the bulbar conjunctiva remote from the limbus; sludging in all superficial and deep vessels; and

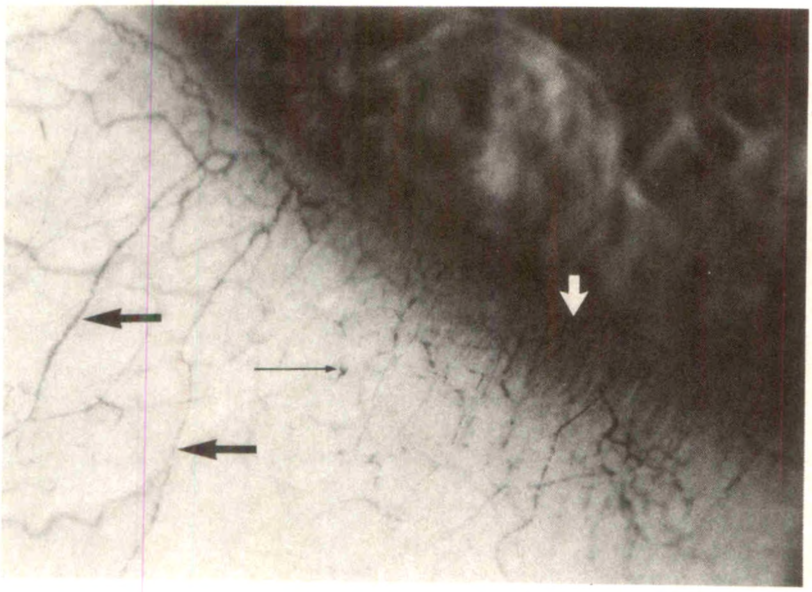


Figure (Engstrom and associates). The conjunctiva of a patient with human immunodeficiency virus infection showing dilated capillaries at the limbus (white arrow), isolated vascular fragments (small black arrow), and granularity of the blood column (large black arrow). Flow of the granular blood column was slow. The patient received a conjunctival microvasculopathy score of severe.

marked slowing of blood flow, with or without stasis in limbal capillaries.

Patients whose disease did not correspond exactly with these definitions were assigned the score that most closely described their condition. Neither blood-flow sludging nor changes in vessel structure were given greater weight in assigning patients to each group.

In cases with asymmetric findings, assigned scores were based on the eye with the more severe disease. Two patients had a known history of unilateral herpes simplex virus keratitis. Only the eye without corneal disease was used to evaluate the degree of microvasculopathy in these two patients.

After biomicroscopic examination, pupils were dilated and retinas of both eyes were examined by indirect ophthalmoscopy for the presence of cotton-wool spots. All findings and scores were recorded at the time of examination before knowledge of laboratory results.

Laboratory studies—For each patient, the following values were obtained: hematocrit level, Westergren erythrocyte sedimentation rate, zeta sedimentation ratio, fibrinogen level, plasma viscosity (relative to water at 37 C as measured on a cone-plate viscometer), circulating immune complexes (by Raji cell assay), and quantitative immunoglobulins (IgG, IgM, IgA). Zeta sedimentation ratio, a hematocrit-independent measure of red cell aggregation,[22-25] was performed in addition to Westergren erythrocyte sedimentation rate because of the potential for hematocrit-induced error in the latter test.[24,26]

Venous blood from an antecubital vein was drawn through a 20-gauge needle into a 40-ml syringe without anticoagulant, after the release of the tourniquet, for more than five seconds to minimize stasis effects on viscosity. For tests to be performed on plasma, blood was immediately transferred into the appropriate anticoagulant: ethylenediaminetetraacetate for hematocrit level and zeta sedimentation ratio; sodium citrate for Westergren erythrocyte sedimentation rate and fibrinogen level; and sodium heparin for plasma viscosity. Raji cell assay for circulating immune complex levels and quantitative immunoglobulin testing were performed on the serum.

Hematocrit levels and zeta sedimentation ratio were determined by us in a masked fashion immediately after drawing blood, using a Zetafuge and microhematocrit centrifuge, as previously described.[22]

Statistical analysis—A Fisher exact test was used to assess the association between disease severity (blood-flow sludging, changes in vessel structure, and the presence of cotton-wool spots) and the following parameters: each of the other measures of disease severity, stage of human immunodeficiency virus–related illness, history of *Pneumocystis carinii* pneumonia, zidovudine use, and the presence of detectable circulating immune complexes. The relationship between conjunctival microvasculopathy scores and the same parameters was investigated with the chi-square test for linear trends. Differences in mean values for the following parameters between patients grouped by mea-

sures of disease severity were assessed with a one-way analysis of variance (if all groups had equal variances) or the Welch equality of means test (if groups had unequal variances based on Levene test for equality of variances): interval since human immunodeficiency virus infection was diagnosed, hematocrit, zeta sedimentation rate, Westergren erythrocyte sedimentation rate, fibrinogen level, plasma viscosity, IgG, IgM, and IgA. Pairwise comparisons were also made between the conjunctival microvasculopathy scores by t-tests that utilized the analysis of variance test estimate for the variance. Significance levels for these t-tests were based on the Bonferroni inequality. A Pearson correlation coefficient was used to assess the relationship between hematocrit level and both zeta sedimentation ratio and Westergren erythrocyte sedimentation. The relationship between Westergren erythrocyte sedimentation rate and the following parameters was investigated with an analysis of covariance that controlled for differences in hematocrit level: blood-flow sludging, changes in vessel structure, conjunctival microvasculopathy score, and the presence of cotton-wool spots. The association between the hematocrit level and the same parameters was assessed by means of a two-way analysis of variance that controlled for the stage of human immunodeficiency virus–related illness. A two-sample t-test using pooled variance was used to compare hematocrit to blood-flow sludging, changes in vessel structure, conjunctival microvasculopathy score, the presence of cotton-wool spots, the stage of human immunodeficiency virus–related illness, and zidovudine use, and to compare zeta sedimentation ratio, Westergren erythrocyte sedimentation rate, and fibrinogen level to the stage of human immunodeficiency virus–related illness. A significance level of .05 was used. All statistical tests used were appropriate for analyzing small sample sizes. Groups for all t-tests and analysis of variances included at least four subjects.

Results

The mean age of the patients was 37 years (range, 24 to 58 years). Ten patients (45%) had AIDS; nine (41%) had AIDS-related complex; and three (14%) were asymptomatic human immunodeficiency virus–infected individuals. The diagnosis of AIDS was based on a history of *P. carinii* pneumonia in seven patients, on the presence of Kaposi sarcoma in two patients, and on a history of cryptococcal meningitis in one patient. None had clinically apparent opportunistic infections at the time of examination. The median interval since diagnosis of human immunodeficiency virus infection was 20 months (range, three to 48 months). Fifteen patients (68%) were taking zidovudine.

There were significant associations between all measures of conjunctival disease severity: blood-flow sludging and changes in vessel structure (P = .03); conjunctival microvasculopathy score and blood-flow sludging (P = .01); and conjunctival microvasculopathy score and changes in vessel structure (P = .001).

There was an trend, although not statistically significant (P = .06), between severity of conjunctival microvasculopathy score and a diagnosis of AIDS. No significant relationships were identified between any measure of conjunctival disease severity and other potentially confounding variables, including the presence of cotton-wool spots, interval since human immunodeficiency virus infection was diagnosed, history of *P. carinii* pneumonia, or zidovudine use.

The prevalence of cotton-wool spots in patients with AIDS (seven of ten patients, 70%) was significantly higher than in other human immunodeficiency virus–infected individuals (two of 12 patients, 17%, P = .03). No significant relationships were identified between cotton-wool spots and the interval since human immunodeficiency virus infection was diagnosed, history of *P. carinii* pneumonia, or zidovudine use.

Mean values for all patients in the study were above normal for Westergren erythrocyte sedimentation rate (32 mm/hr; normal, 0 to 15 mm/hr), zeta sedimentation ratio (0.65; normal, 0.46 to 0.58), plasma viscosity (2.4 relative to water; normal, 1.5 to 1.9), and IgG (1,571 mg/dl; normal, 650 to 1,449 mg/dl). Mean values were within normal ranges for fibrinogen (326 mg/dl; normal, 200 to 400 mg/dl), IgM (117 mg/dl; normal, 28 to 207 mg/dl), and IgA (274 mg/dl; normal, 75 to 326 mg/dl). Only two patients had circulating immune complex levels detectable above 12 μg/ml. The mean hematocrit for all patients (37%) was below normal (40% to 54%) for adult males.

A lower hematocrit was associated with a diagnosis of AIDS; patients with AIDS had a mean hematocrit of 33%, whereas patients with AIDS-related complex or asymptomatic human immunodeficiency virus infection had a mean hematocrit level of 40% (P = .004). The hema-

tocrit level was not associated with zidovudine use. No associations were identified between Westergren erythrocyte sedimentation rate, zeta sedimentation rate, or fibrinogen, and a diagnosis of AIDS.

The Table lists selected laboratory values for patients grouped by ophthalmic findings. More severe blood-flow sludging was associated with increased zeta sedimentation ratio (P = .002), increased Westergren erythrocyte sedimentation rate (P = .02), and increased fibrinogen (P = .03). More severe changes in vessel structure were associated with increased zeta sedimentation ratio (P = .02), increased Westergren erythrocyte sedimentation rate (P = .03), increased fibrinogen (P = .02), and decreased hematocrit (P = .05). Worse conjunctival microvasculopathy scores were related to increased zeta sedimentation ratio (P = .05 overall, P = .02 between mild and severe scores), increased fibrinogen (P = .04 overall, P = .02 between mild and moderate scores), and detectable circulating immune complex levels (P = .04 overall), but not to Westergren erythrocyte sedimentation rate. No measure of conjunctival disease severity was associated with increased plasma viscosity or immunoglobulin levels.

Cotton-wool spots were associated with increased Westergren erythrocyte sedimentation rate (P = .03) and increased fibrinogen (P = .04), but not with increased zeta sedimentation ratio. There was a trend, although not statistically significant (P = .06), toward decreased hematocrit levels in patients with cotton-wool spots. Westergren erythrocyte sedimentation rate was inversely correlated with hematocrit (Pearson $r = -0.74$, 95% confidence limits = [−0.89, −0.45], P < .001), whereas zeta sedimentation ratio was not correlated (Pearson $r = -0.35$, P = .11). The association between cotton-wool spots and hematocrit level did not become stronger when analysis of covariance was used to control for the influence of a diagnosis of AIDS. No association was found between cotton-wool spots and Westergren erythrocyte sedimentation rate when an analysis of

TABLE

LABORATORY FINDINGS IN PATIENTS WITH HUMAN IMMUNODEFICIENCY VIRUS INFECTION AND MICROVASCULOPATHY*

PARAMETER	NO. OF PATIENTS	WESTERGREN ERYTHROCYTE SEDIMENTATION RATE (MM/HR)	ZETA SEDIMENTATION RATIO	HEMATOCRIT LEVEL (%)	FIBRINOGEN LEVEL (MG/DL)
Normal ranges	—	0–15	0.46–0.58	40–54	200–400
All patients	22	32 (± 32)	0.65 (± 0.07)	37 (± 6)	326 (± 98)
Severity of conjunctival blood-flow sludging					
1+ (mild)	9	13 (± 13)†	0.60 (± 0.06)†	39 (± 5)	270 (± 46)†
2+ (severe)	13	46 (± 35)†	0.68 (± 0.05)†	35 (± 6)	364 (± 106)†
Severity of changes in conjunctival vessel structure					
1+ (mild)	13	19 (± 16)†	0.62 (± 0.06)†	39 (± 5)†	282 (± 57)†
2+ (severe)	9	49 (± 40)†	0.69 (± 0.06)†	34 (± 5)†	381 (± 113)†
Conjunctival microvasculopathy score					
Mild	5	11 (± 14)†	0.60 (± 0.07)†	41 (± 4)	249 (± 35)†
Moderate	12	28 (± 19)†	0.65 (± 0.05)†	36 (± 6)	315 (± 51)†
Severe	5	59 (± 50)†	0.70 (± 0.07)†	35 (± 6)	414 (± 149)†
Cotton-wool spots					
Absent	13	18 (± 19)†,‡	0.63 (± 0.06)	38 (± 5)§	286 (± 54)†
Present	9	50 (± 38)†,‡	0.67 (± 0.08)	34 (± 5)§	375 (± 119)†

*All laboratory values listed as mean (± standard deviation).

†Relationships significant at the 0.05 level (all assessments by one-way analysis of variance or Welch equality of means test).

‡Not significant (P = .12, analysis of covariance) when controlled for influence of hematocrit.

§P = .06, one-way analysis of variance.

covariance was used to control for the influence of hematocrit (P = .12). No association was identified between cotton-wool spots and increased plasma viscosity, the presence of increased circulating immune complexes, or increased immunoglobulin levels. A history of cotton-wool spots in patients without retinal lesions at the time of examination was not considered in the analyses.

Discussion

Microvascular disease is a common feature of human immunodeficiency virus infection. Ultrastructural changes are identified in retinal vessels of 88% to 100% of patients and include loss and degeneration of pericytes, swollen endothelial cells, thickened basal laminae, and narrowed capillary lumina.[2,3] Clinically apparent sequelae include cotton-wool spots (27% to 71% ofpatients[1,2,27,28]), retinal hemorrhages (8% to 40% of patients[2,27]), microaneurysms,[2] and microvascular anomalies on fluorescein angiography.[3]

Conjunctival microvascular changes were reported in 75% of human immunodeficiency virus–infected patients in a small series,[4] but it is our experience that these changes occur in all human immunodeficiency virus–infected patients to some degree. Alterations in blood flow, seen within arterioles, capillaries, and venules, include a granular appearance to the blood column, attributable to the aggregation of red blood cells and decreased rates of flow. These alterations are most obvious in small perilimbal vessels, but can be seen in larger vessels throughout the conjunctiva in more severe cases. Changes in vessel structure, observed by biomicroscopy in capillaries and small venules, include capillary dilation, microaneurysms, isolated vessel fragments, and short vessel segments of irregular caliber. Changes are most apparent on the inferior, perilimbal, bulbar conjunctiva (Figure).

The clinical significance of microvascular disease in patients with human immunodeficiency virus infection remains uncertain. As in this study, other investigators have shown a relationship between the presence of cotton-wool spots and more severe forms of human immunodeficiency virus–induced disease.[29,30] Limited evidence also suggests that cotton-wool spots indicate a poor prognosis, because they are associated with an increased incidence of opportunistic infection and increased mortality.[1,31] Most microvascular lesions are clinically insignificant, but, rarely vision-threatening macular ischemia occurs.[2] Also it has been hypothesized that vascular damage may increase one's susceptibility to the development of cytomegalovirus retinopathy by allowing access of viral particles to retinal tissue through damaged vessel walls.[2,28] Furthermore, the eye may reflect widespread microvascular disease. Nonocular vascular abnormalities, such as cutaneous telangiectasias, characterized histologically by dilated vascular segments, also have been described in human immunodeficiency virus–infected patients.[32] The eye, and especially the conjunctiva because of its accessibility, may serve as a convenient model for study of diffuse vascular disease.

The cause of microvascular disease in patients with AIDS is unknown. Deposition of circulating immune complexes[2] and infection of vascular endothelial cells with human immunodeficiency virus[33,34] are proposed causes, but the importance of these factors in disease pathogenesis has not been established. Infection of vascular endothelial cells by human immunodeficiency virus does not explain the marked similarities between the microvasculopathy associated with human immunodeficiency virus infection and that seen in a diverse group of other diseases.

Ultrastructural changes in the retinal microvasculature and fluorescein angiographic findings are similar to those seen with diabetes mellitus.[3] Cotton-wool spots and nonembolic arteriolar and capillary occlusions develop in patients with systemic lupus erythematosus.[7] Retinal microaneurysms are observed frequently in patients with leukemia.[6,7] Conjunctival microvascular changes occur in sickle cell disease,[11-14] chronic myelogenous leukemia,[15] and ataxia-telangiectasia.[16,17]

Alteration of blood flow is commonly hypothesized to be a factor in the pathogenesis of microvasculopathy in many diseases. Generally, red blood cell aggregation is the most important cause of anomalous hemorheologic properties.[35] It results from nonspecific bridging between adjacent cells by plasma proteins, of which fibrinogen is the most important.[36] At equal concentrations, the larger the protein molecule, and in particular the more aspherical its shape, the greater will be its effect on cellular aggregation and viscosity.[37] Fibrinogen (an asymmetric molecule) has a molecular weight approximately twice that of the immunoglobu-

lins, but has 20 times the influence of the immunoglobulins on cell-cell interactions.[38] Red cell aggregation is increased in patients with diabetes.[39] Increases in red blood cell aggregation and in fibrinogen levels have been shown to be associated with increasing severity of diabetic retinopathy.[40] Fibrinogen also is increased as an acute phase reactant during sickle cell crises.[41] The cause remains unknown.

Fibrinogen may be the factor most responsible for the hyperviscous state and increased red cell aggregation observed in human immunodeficiency virus–infected patients. In this study, associations existed between fibrinogen levels and each measure of disease severity: conjunctival microvasculopathy score, blood-flow sludging, change in vessel structure, and the presence of cotton-wool spots. The cause of increased fibrinogen levels in patients with human immunodeficiency virus infection remains unknown.

Other factors that can contribute to increased red blood cell aggregation and abnormal blood flow are increased circulating immune complex levels and increased immunoglobulin levels, both of which may occur in patients with AIDS.[42] The Raji cell assay is reported to be a sensitive measure of circulating immune complex levels in patients with AIDS.[43] This technique showed detectably increased circulating immune complex levels in only two patients and was associated with only the conjunctival microvasculopathy score. The prevalence of increased circulating immune complex levels in this study was lower than previously reported for AIDS patients with ocular disease[1,44]; this discrepancy may be related to the fact that all patients in this study were ambulatory, whereas previous studies involved seriously ill, hospitalized patients.

Patients with AIDS may have selective increases in immunoglobulin subclasses, including IgG, IgM,[42] or IgA.[45] In this study, mean IgG levels were increased for each of the conjuctival microvasculopathy score groups, but significant statistical differences were not observed between groups. Mean levels of IgM and IgA for all patients were not increased.

Sedimentation rates provide an estimate of red cell aggregation. Higher rates are associated with increases in acute phase reactants. The zeta sedimentation ratio is a less commonly used, although potentially more accurate, measure of red blood cell aggregation than the Westergren erythrocyte sedimentation rate.[23] Both the Westergren and Wintrobe methods for determining erythrocyte sedimentation rate are hematocrit-dependent,[24,26] whereas the zeta sedimentation ratio is hematocrit-independent.[24,25] The zeta sedimentation ratio increases with increasing red cell aggregation and its response is linear with increases in fibrinogen and gamma globulin.[22]

Blood-flow sludging may contribute to the development of clinically apparent changes in vessel structure. As sludging increases, the delivery of oxygen at the capillary level is compromised because of stasis and vascular blockage by red cell aggregates.[46] It has been hypothesized that hypoxia related to abnormal blood flow causes microangiopathic changes in vessels.[47] Stasis of blood flow has been implicated as a contributing factor in the saccular dilation of vessels in patients with sickle cell disease.[13] Hypoxia creates an environment that appears to stimulate the development of retinal microaneurysms.[48] The relationship between severe blood flow sludging and severe changes in vessel structure among patients in this study supports the conclusion that they are interdependent phenomena. Anemia may be an additional contributor to hypoxia and vessel damage; lower hematocrit levels were associated with changes in vessel structure.

The relationship between lower hematocrit levels and the presence of cotton-wool spots suggests that anemia may also contribute to cotton-wool spot formation, possibly by increasing the hypoxia associated with preexisting microvascular insufficiency. The observed association between the Westergren erythrocyte sedimentation rate and cotton-wool spots, therefore, may be a reflection of lower hematocrit levels rather than a true relationship with increased red cell aggregation, especially because an association was not observed with the hematocrit-independent zeta sedimentation ratio. That there was not a strong relationship between hematocrit level and cotton-wool spots may reflect that these transient lesions are the result of ischemic events that occurred up to six weeks before discovery on examination.

The significance of the relationship between decreased hematocrit levels and microvasculopathy is uncertain. Both hematocrit level and the presence of cotton-wool spots were related to the stage of human immunodeficiency virus–related disease, and there was a trend between a diagnosis of AIDS and severe conjunctival microvasculopathy scores. The relationships between hematocrit level and cotton-wool spots and between hematocrit level and changes in

vessel structure did not remain significant, however, when analysis of covariance was used to control for the influence of a diagnosis of AIDS. A study involving more patients will be needed to assess more accurately these complex interrelationships; the lack of significant associations between some measures in this pilot study may reflect low power from small sample sizes.

The results of this study are consistent with the following hypotheses. Increased fibrinogen levels in human immunodeficiency virus–infected patients contribute to sludging of blood flow by increasing red blood cell aggregation. Sludging of blood flow (probably in association with other factors) causes vascular damage of the conjunctival and possibly the retinal microvasculature. Anemia or other unknown factors lead to transient episodes of increased ischemia sufficient to produce cotton-wool spots in patients with preexisting blood-flow sludging and vascular damage. Further investigation of hemorheologic factors may be useful toward gaining a better understanding of the microvasculopathy associated with human immunodeficiency virus infection.

ACKNOWLEDGMENTS

Sarah B. Forsythe, M.S. and Noel C. Wheeler, Ph.D. of the UCLA Department of Biomathematics performed the statistical analysis of data. Westergren erythrocyte sedimentation rate, fibrinogen levels, and quantitative immunoglobulin determination were performed by the UCLA Clinical Laboratories, and the Raji cell assay for circulating immune complex levels was performed at Specialty Laboratories, Santa Monica, California. Plasma viscosity relative to water was determined at 37 C by means of a cone-plate viscometer (model LVT, Brookfield Engineering, Stoughton, Massachusetts) at the Smith-Kline Biosciences Laboratories, Van Nuys, California.

References

1. Holland, G. N., Pepose, J. S., Pettit, T. H., Gottlieb, M. S., Yee, R. D., and Foos, R. Y.: Acquired immune deficiency syndrome. Ocular manifestations. Ophthalmology 90:859, 1983.

2. Pepose, J. S., Holland, G. N., Nestor, M. S., Cochran, A. J., and Foos, R. Y.: Acquired immune deficiency syndrome. Pathogenic mechanisms of ocular disease. Ophthalmology 92:472, 1985.

3. Newsome, D. A., Green, W. R., Miller, E. D., Kiessling, L. A., Morgan, B., Jabs, D. A., and Polk, B. F.: Microvascular aspects of acquired immune deficiency syndrome retinopathy. Am. J. Ophthalmol. 98:590, 1984.

4. Teich, S. A.: Conjunctival vascular changes in AIDS and AIDS-related complex. Am. J. Ophthalmol. 103:332, 1987.

5. Jampol, L. M., Goldberg, M. F., and Busse, B.: Peripheral retinal microaneurysms in chronic leukemia. Am. J. Ophthalmol. 80:242, 1975.

6. Duke, J. R., Wilkinson, C. P., and Sigelman, S.: Retinal microaneurysms in leukaemia. Br. J. Ophthalmol. 52:368, 1968.

7. Santos, R., Barojas, E., Alarcon-Segovia, D., and Ibanez, G.: Retinal microangiopathy in systemic lupus erythematosus. Am. J. Ophthalmol. 80:249, 1975.

8. Ashton, N.: Ocular changes in multiple myelomatosis. Arch. Ophthalmol. 73:487, 1965.

9. Sanders, T. E., Podos, S. M., and Rosenbaum, L. J.: Intraocular manifestations of multiple myeloma. Arch. Ophthalmol. 77:789, 1967.

10. Paton, D.: The conjunctival sign of sickle-cell disease. Arch. Ophthalmol. 68:627, 1962.

11. Serjeant, G. R., Serjeant, B. E., and Condon, P. I.: The conjunctival sign in sickle cell anemia. A relationship with irreversibly sickled cells. JAMA 219:1428, 1972.

12. Nagpal, K. C., Goldberg, M. F., and Rabb, M. F.: Ocular manifestations of sickle hemoglobinopathies. Surv. Ophthalmol. 21:391, 1977.

13. Funahashi, T., Fink, A., Robinson, M., and Watson, R. J.: Pathology of conjunctival vessels in sickle-cell disease. Am. J. Ophthalmol. 57:713, 1964.

14. Fink, A. I., Funahashi, T., Robinson, M., and Watson, R. J.: Conjunctival blood flow in sickle-cell disease. Arch Ophthalmol 66:824, 1961.

15. Swartz, M., and Jampol, L. M.: Comma-shaped venular segments of conjunctiva in chronic granulocytic leukemia. Can. J. Ophthalmol. 10:458, 1975.

16. Kulikov, V. V.: Changes in the microvascular bed of the conjunctiva of the eyes in ataxia-telangiectasia. Arkhiv. Patologii. 36:30, 1974.

17. Harley, R. D., Baird, H. W., and Craven, E. M.: Ataxia-telangiectasia. Report of seven cases. Arch. Ophthalmol. 77:582, 1977.

18. Lowe, G. D O.: Blood rheology in general medicine and surgery. Baillieres Clin. Haematol. 1:827, 1987.

19. Centers for Disease Control: Revision of the Centers for Disease Control surveillance case definition for acquired immunodeficiency syndrome. MMWR 36:1S, 1987.

20. Kwok, S., O'Donnell, J. J., and Wood, I. S.: Retinal cotton-wool spots in a patient with *Pneumocystis carinii* infection. N. Engl. J. Med. 307:184, 1982.

21. Fischl, M. A., Richman, D. D., Grieco, M. H., Gottlieb, M. S., Volberding, P. A., Laskin, O. L., Leedon, J. M., Groopman, J. E., Mildvan, D.,

Schooley, R. T., Jackson, G. G., Durack, D. T., and King, D. (The AZT Collaborative Working Group): The efficacy of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex. N. Engl. J. Med. 317:185, 1987.

22. Bull, B. S., and Brailsford, J. D.: The zeta sedimentation ratio. Blood 40:550, 1972.

23. Seaman, G. V F., Corry, W. D., Blume, P., and Jackson, L.: Theoretical bases for the role of erythrocyte sedimentation rate, plasma viscosity and zeta sedimentation ratio measurements in clinical medicine. Clin. Hemorheol. 1:87, 1981.

24. Love, D. C., Berler, D. K., O'Dowd, G. J., and Brooks, J. Z.: Erythrocyte sedimentation rate and its relationship to hematocrit giant cell arteritis. Arch. Ophthalmol. 106:309, 1988.

25. Talkers, R.: Erythrocyte sedimentation rate/zeta sedimentation ratio. Emerg. Med. Clin. North Am. 4:87, 1986.

26. Jacobson, D. M., and Slamovits, T. L.: Erythrocyte sedimentation rate and its relationship to hematocrit in giant cell arteritis. Arch. Ophthalmol. 105:965, 1987.

27. Freeman, W. R., Lerner, C. W., Mines, J. A., Lash, R. S., and Nadel, A. J.: A prospective study of the ophthalmologic findings in the acquired immune deficiency syndrome. Am. J. Ophthalmol. 97:133, 1984.

28. Palestine, A. G., Rodrigues, M. M., Macher, A. M., Chan, C.-C., Lane, H. C., Fauci, A. S., Masur, H., Longo, D., Reichert, C. M., Steis, R., Rook, A. H., and Nussenblatt, R. B.: Ophthalmic involvement in acquired immunodeficiency syndrome. Ophthalmology 91:1092, 1984.

29. Freeman, W. R., Chen, A., Henderly, D. E., Levine, A. M., Luttrull, J. K., Urrea, P. T., Arthur, J., Rasheed, S., Cohen, J. L., Neuberg, D., and Leung, R. J.: Prevalence and significance of acquired immunodeficiency syndrome–related retinal microvasculopathy. Am. J. Ophthalmol. 107:229, 1989.

30. Jabs, D. A., Enger, C., and Bartlett, J. G.: Cytomegalovirus retinitis and acquired immunodeficiency syndrome. Arch. Ophthalmol. 107:75, 1989.

31. Humphry, R. C., Weber, J. N., and Marsh, R. J.: Ophthalmic findings in a group of ambulatory patients infected by human immunodeficiency virus (HIV). A prospective study. Br. J. Ophthalmol. 71:565, 1987.

32. Fallon, T., Abell, E., Kingsley, L., Ho, M., Winklestein, A., Jensen, F., and Rinaldo, C.: Telangiectasias of the anterior chest in homosexual men. Ann. Intern. Med. 105:679, 1986.

33. Pomerantz, R. J., Kuritzkes, D. R., de la Monte, S. M., Rota, T. R., Baker, A. S., Albert, D., Bor, D. H., Feldman, E. L., Schooley, R. T., and Hirsch, M. S.: Infection of the retina by human immunodeficiency virus type I. N. Engl. J. Med. 317:1643, 1987.

34. Cantrill, H. L., Henry, K., Jackson, B., Erice, A., Ussery, F. M., and Balfour, H. H.: Recovery of human immunodeficiency virus from ocular tissues in patients with acquired immune deficiency syndrome. Ophthalmology 95:1458, 1988.

35. Replogle, R. L., Meiselman, H. J., and Merrill, E. W.: Clinical implications of blood rheology studies. Circulation 36:148, 1967.

36. Ozanne, P., Linderkamp, O., Miller, F. C., and Meiselman, H. J.: Erythrocyte aggregation during normal pregnancy. Am. J. Obstet. Gynecol. 147:576, 1983.

37. Harkness, J.: The viscosity of human blood plasma. Its measurement in health and disease. Biorheology 8:171, 1971.

38. Chien, S., Usami, S., Dellenback, R. J., and Gregersen, M. I.: Shear-dependent interaction of plasma proteins with erythrocytes in blood rheology. Am. J. Physiol. 219:143, 1970.

39. Bauersachs, R., Zeidler, A., Don, D., Ribitsch, V., and Meiselman, H.: RBC aggregation and blood viscoelasticity in type II diabetes mellitus. Diabetes 35:105A, 1986.

40. Little, H. L., and Sacks, A. H.: Role of abnormal blood rheology in the pathogenesis of diabetic retinopathy. Trans. Am. Acad. Ophthalmol. Otolaryngol. 83:522, 1977.

41. Lawrence, C., and Fabry, M. E.: Erythrocyte sedimentation rate during steady state and painful crisis in sickle cell anemia. Am. J. Med. 81:801, 1986.

42. Euler, H. H., Kern, P., Loffler, H., and Dietrich, M.: Precipitable immune complexes in healthy homosexual men, acquired immune deficiency syndrome and the related lymphadenopathy syndrome. Clin. Exp. Immunol. 59:267, 1985.

43. Gupta, S., and Licorish, K.: Circulating immune complexes in AIDS. N. Engl. J. Med. 310:1530, 1984.

44. Holland, G. N., Gottlieb, M. S., Yee, R. D., Schanker, H. M., and Pettit, T. H.: Ocular disorders associated with a new severe acquired cellular immunodeficiency syndrome. Am. J. Ophthalmol. 93:393, 1982.

45. Lightfoote, M. M., Folks, T. M., Redfield, R., Gold, J., and Sell, K. W.: Circulating IgA immune complexes in AIDS. Immunol. Invest. 14:341, 1985.

46. Knisely, M. H., Bloch, E. H., Eliot, T. S., and Warner, L.: Sludged blood. Science 106:431, 1947.

47. Ditzel, J.: Changes in red cell oxygen release capacity in diabetes mellitus. Fed. Proc. 38:2484, 1979.

48. Yanoff, M: Ocular pathology of diabetes mellitus. Am. J. Ophthalmol. 67:21, 1969.

Corneal Topography of Patients With Excellent Snellen Visual Acuity After Epikeratophakia for Aphakia

Leo J. Maguire, M.D.

A computer-based corneal topographic analysis system was used to evaluate the patterns of power distribution in five patients with at least six months of postoperative follow-up who obtained excellent visual and refractive results after epikeratophakia for aphakia. All grafts were well centered relative to the visual axis. The range of surface power seen within the central 5 mm of the individual grafts ranged from 4.00 to 6.50 diopters. Each graft showed a unique, moderately irregular pattern of power distribution. Fair correlation was seen between the expected corneal power and that shown in the power map displays. These data suggest that moderate degrees of irregular astigmatism are compatible with good Snellen visual acuity after epikeratophakia for aphakia, though the effect of this irregularity on visual performance remains unclear.

Little information exists on the quality of corneal surface topography after epikeratophakia for aphakia. It is known that sensitive computer-based corneal topographic analysis systems are useful in identifying differences between predicted and achieved surface topography patterns after epikeratophakia for myopia. Myopic grafts, even those that allowed excellent Snellen visual acuity, were found to have a small central island of uniform power surrounded by a highly irregular peripheral graft whose power rapidly increased as the graft edge was approached.[1] This study addresses whether patients with excellent Snellen visual acuity after epikeratophakia for aphakia have a characteristic pattern of power distribution.

Material and Methods

A chart review was performed on all patients who had undergone epikeratophakia for aphakia by me between August 1986 and March 1988. Examination of preoperative data identified eight patients with a normal fixation pattern, visual acuity greater than or equal to 20/30, and ≤2.50 diopters of keratometric astigmatism (Table 1). Manifest refraction and visual acuity measurements were performed by an independent observer on these seven patients at the first regularly scheduled postoperative visit that occurred after the arrival of the Corneal Modeling System[2] at the Mayo Clinic in May 1988. All patients who met the inclusion criteria for an excellent postoperative refractive result (best-corrected visual acuity greater than or equal to 20/30, manifest refraction within 3 diopters of emmetropia, and <2.50 diopters of refractive astigmatism) at that visit were analyzed with the Corneal Modeling System. Of the eight patients with preoperative visual potential of 20/30 or better, five met the postoperative entry criteria (Table 2).

Four keratoscopic video images were made of each eye. The technician did not save for computer memory any image for which the aiming laser images were not exactly superimposed, any image in which patient fixation was in doubt, or any image showing evidence of tear film artifact.

The video images were processed using the Corneal Modeling System software program 1.1. Errors made in the autodigitizing process were noted. The video images were ranked in order of overall quality, taking into considera-

Accepted for publication Oct. 10, 1989.

From the Department of Ophthalmology, Mayo Clinic and Foundation, Rochester, Minnesota. This study was supported in part by the Mayo Foundation, Rochester, Minnesota. This study was presented at the Association for Research in Vision and Ophthalmology meeting, Sarasota, Florida, May 1, 1989.

Reprint requests to Leo J. Maguire, M.D., Department of Ophthalmology, Mayo Foundation, 200 First St. S.W., Rochester, MN 55905.

tion the amount of surface area covered by the keratoscope mires and the quality of the auto-digitizing process. The image with the highest rank was used to generate the color-coded topographic maps. No keratoscopic image was accepted for analysis if inaccurate digitization of any of the central 17 rings was observed.

To allow sensitive evaluation of the surface topography, a 0.5-diopter range of surface power was assigned to each color in the contour map scheme. The range and pattern of power distribution within the central 5-mm zone were evaluated. The dioptric values generated by the contour maps were compared with the power values that would be expected if regular astigmatism of the postoperative corneal surface were assumed. These values were predicted by the following formula: [(average preoperative keratometry) + (keratolens power)] − (residual refractive error) (Table 2).

Results

Keratoscopic images of the epikeratophakia surface were obtained from four of five patients. A prominent brow and recessed globe prevented the capture of a well-focused keratoscopic image in Patient 1. Accurate digitization of rings 1 to 17 (corresponding to the central 5 mm of the graft) was possible in the remaining four patients. All four patients showed good centration of the graft relative to the patient's visual axis. The keratoscopic image of Patient 4, shown in Figure 1, is representative of the keratoscopic images of the other three patients. The central mires are sharply focused. The mires within a millimeter of the graft-host interface show more distortion and cannot be reliably digitized.

The color map generated by a computer analysis of Figure 1 is shown in Figure 2. The cursor, located at the 345-degree hemimeridian on ring 17, marks the peripheral border of accurate analysis. Power within the central "optical zone" ranges from 56.00 to 60.00 diopters. The pattern of power distribution can only be described as irregular because the surface has no well-defined major or minor axis. Corneal powers in the contour map are lower than anticipated (Table 2).

The color map generated by a computer analysis of Patient 7 is shown in Figure 3. Power

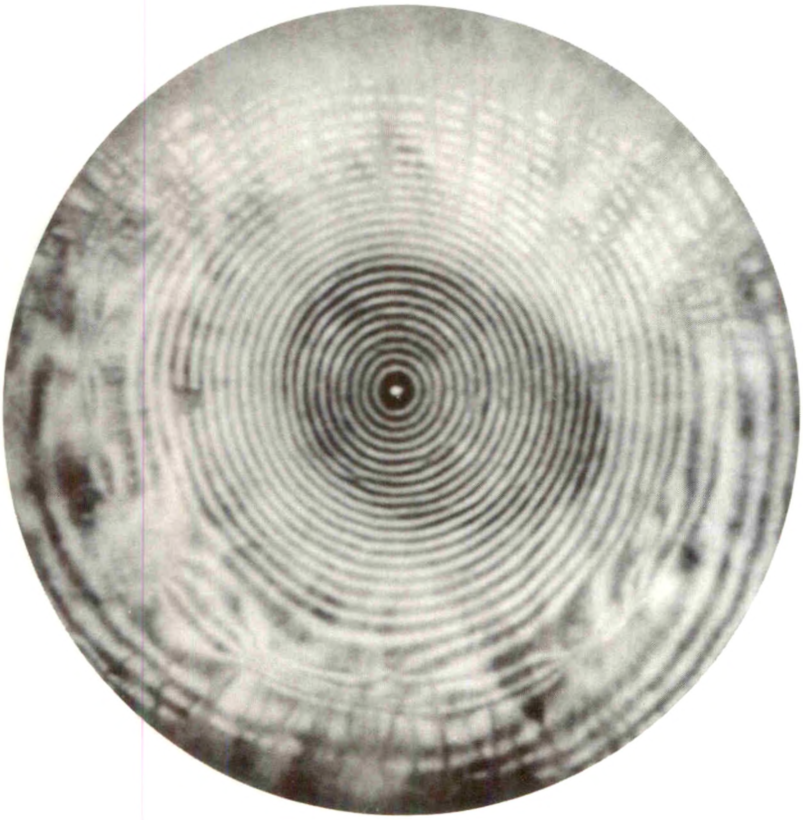


Fig. 1 (Maguire). Keratoscopic image of Patient 4, who had the best refractive accuracy and visual acuity. The central 17 rings, covering an area roughly 5 mm in diameter, are well visualized. Corneal distortion at the graft-host interface precluded accurate analysis past ring 17 in this and the other corneas analyzed in this study.

TABLE 1

PREOPERATIVE AND POSTOPERATIVE REFRACTIVE DATA

	PREOPERATIVE DATA			KERATOLENS INFORMATION		POSTOPERATIVE DATA		
PATIENT NO., EYE, SEX, AGE (YRS)	SPECTACLE REFRACTION	VERTEX	CORRECTED VISUAL ACUITY	AVERAGE KERATOMETRIC READING	POWER	LENGTH OF FOLLOW-UP	SPECTACLE REFRACTION	CORRECTED VISUAL ACUITY
1, R.E., M, 69	+10.00 + 0.75 × 175	17.5	20/25	42.50	+13.00	2 yrs	Plano	20/25
2, R.E., M, 66	+11.50 + 1.00 × 90	10.0	20/20	42.50	+13.50	2 yrs	−1.50 + 4.50 × 85	20/20
3, L.E., F, 75	+12.50	20.0	20/25	44.50	+16.00	19 mos	−3.00 + 2.25 × 110	20/25
4, L.E., M, 49	+11.50	18.0	20/20	44.50	+14.00	18 mos	−2.75 + 1.00 × 134	20/15
5, L.E., M, 78	+9.75 + 1.00 × 180	20.0	20/25	45.00	+13.00	13 mos	−3.25 + 3.25 × 35	20/40
6, R.E., F, 78	+10.00 + 1.50 × 150	14.5	20/25	47.50	+13.00	1 yr	+7.50 + 1.00 × 40	20/30
7, L.E., F, 53	+12.50 + 1.25 × 113	15.0	20/30	42.00	+16.00	1 yr	+1.75 + 1.25 × 132	20/20
8, R.E., M, 59	+8.00 + 2.00 × 155	14.0	20/30	42.50	+10.50	7 mos	+2.00 + 1.50 × 156	20/20

within the central 17 rings varies from 52.00 to 56.50 diopters. The pattern of power distribution is irregular. Expected power for this surface would show a meridian of highest power at 132 degrees with a value of 56.25 diopters, and a meridian of lowest power at 42 degrees with a power of 55.00 diopters.

The power map generated by an analysis of Patient 8 is shown in Figure 4. Power ranges from 45.50 to 51.50 diopters. The topography is irregular, showing a central area of maximum power with areas of lower power toward the periphery of the optical zone. Corneal power at the center of the graft correlates with expected power (Table 2).

Discussion

Although the number of patients included in this study is too small to make generalizations about the topographic characteristics of patients who obtain a good refractive result after epikeratophakia for aphakia, I believe that the study's results are sufficient to offer a working

TABLE 2

PREDICTED VS MEASURED TOPOGRAPHY AFTER EPIKERATOPHAKIA FOR APHAKIA IN PATIENTS WITH EXCELLENT REFRACTIVE RESULTS

	TOPOGRAPHIC ANALYSIS DATA		EXPECTED TOPOGRAPHY (AVERAGE PREOPERATIVE KERATOMETRY + KERATOLENS POWER) − RESIDUAL REFRACTIVE ERROR			
PATIENT NO.	POWER RANGE WITHIN 2.5 MM OF FIXATION (DIOPTERS)	PATTERN OF POWER DISTRIBUTION	LOWEST POWER (DIOPTERS)	MERIDIAN LOW POWER (DEGREES)	HIGHEST POWER (DIOPTERS)	MERIDIAN HIGH POWER (DEGREES)
1	*	—	—	—	—	—
3	54.00–58.50	Irregular	61.25	20	63.50	100
4	56.00–60.00	Irregular	60.25	44	61.25	134
7	52.00–56.50	Irregular	55.00	42	56.25	132
8	45.00–51.50	Irregular	49.50	66	51.00	156

*Prominent orbital rim, recessed globe prevented topography analysis.

TABLE 1 (*Continued*)
PREOPERATIVE AND POSTOPERATIVE REFRACTIVE DATA

INDICATION FOR SURGERY
Unilateral aphakia, diabetes, closed loop intraocular lens L.E.
Unilateral aphakia, endothelial cell count 1,300 cells/mm^2, vitreous to wound
Unilateral aphakia, irregular pupil, vitreous to wound
Unilateral aphakia, contact lens–intolerant in dusty work environment
Severe cystoid macular edema R.E. after extracapsular cataract extraction, intraocular lens implant; contact lens intolerance
Unilateral aphakia, contact lens intolerance, refused secondary implant
Unilateral aphakia, Fuchs' iridocyclitis
Glaucoma, history of retinal detachment, contact lens intolerance

hypothesis. The area of the graft that can act as a reasonable optical surface seems to be approximately 5 mm in diameter. Within that zone, the range of power present can be at least as great as 6.50 diopters and at least as small as 4.00 diopters. The pattern of power distribution within this central zone is irregular, although the aphakic grafts in this study did not show the dramatic change in surface power between 1.5 mm and 2.5 mm from the center point of the graft seen in the study of epikeratophakia for myopia.[1] Finally, the corneal powers one would expect to find at the aphakic epikeratophakia surface (predicted power minus residual refractive error) appear to roughly approximate the values displayed in the color-coded power maps.

The clinical relevance of this pilot study is not clear. Some might argue that the presence of variable degrees of corneal irregularity among patients with the best refractive results is a point against the more widespread use of epikeratophakia for aphakia. Others might argue

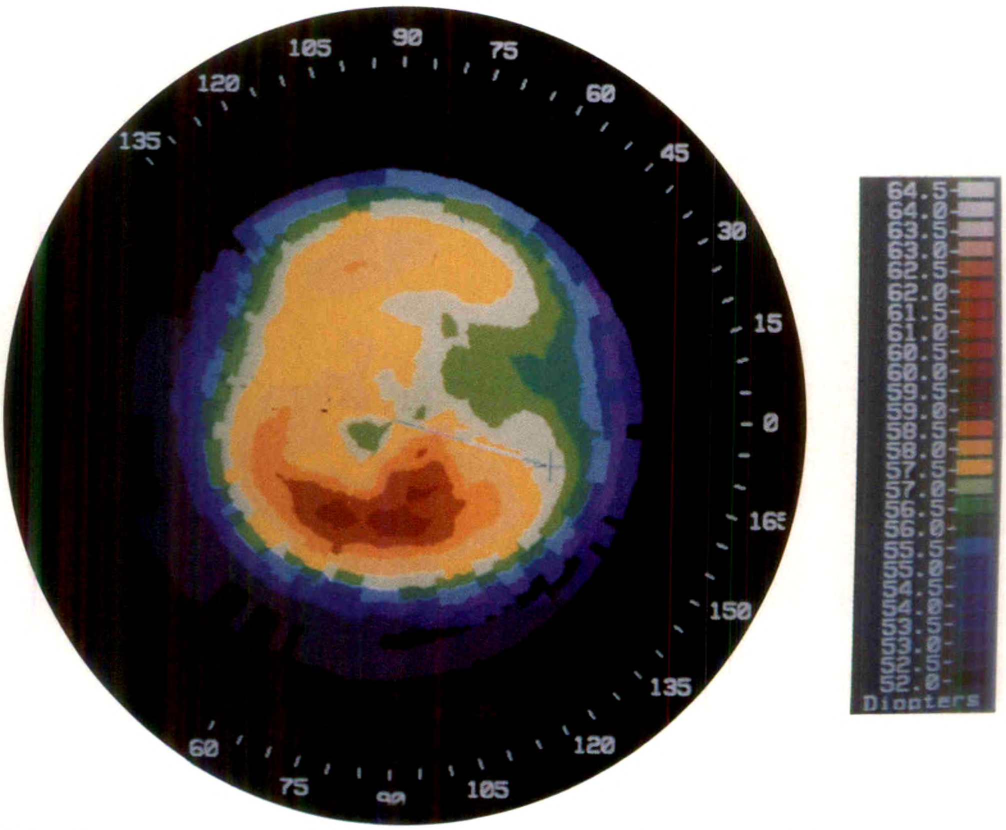


Fig. 2 (Maguire). Color-coded map generated from a computer analysis of Figure 1. Each color represents a 0.5-diopter range of power. The cursor marks the location of ring 17. Within the central 17 rings, power ranges from 56.00 to 60.00 diopters. The pattern of power distribution is irregular with no well-defined flat or steep axis.

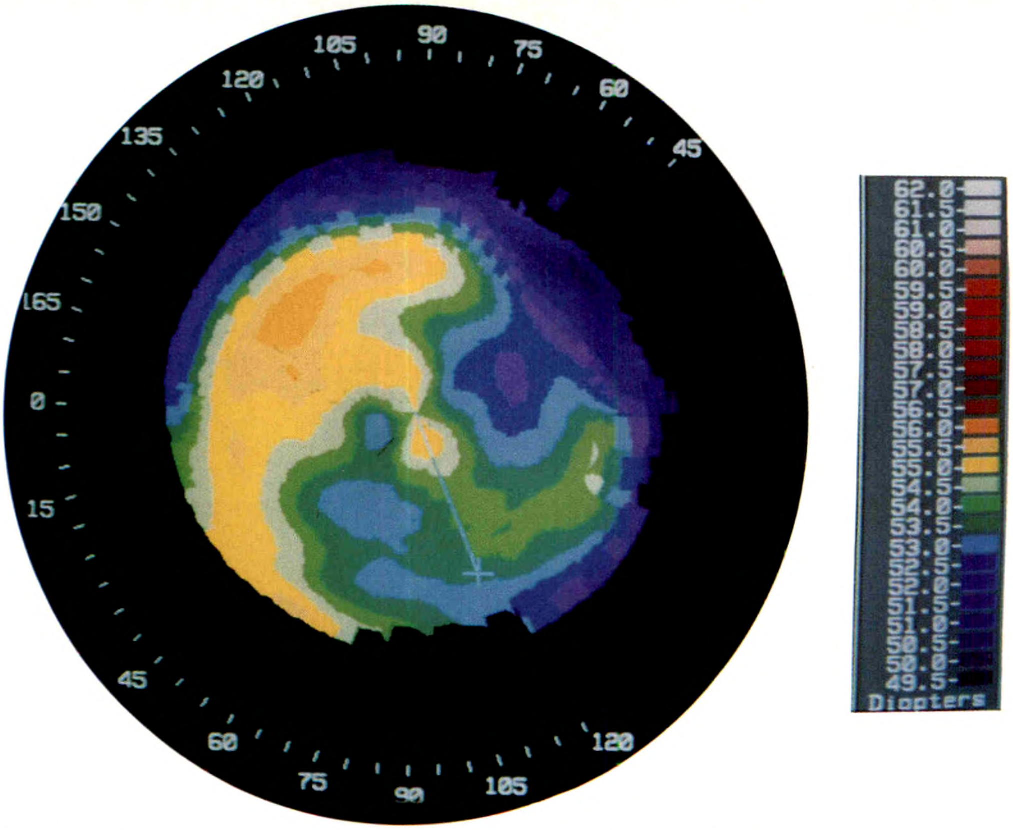


Fig. 3 (Maguire). Topographic analysis of Patient 7. Each color represents a 0.5-diopter range of power. Power ranges from 52.00 to 56.50 diopters and the pattern of power distribution is irregular.

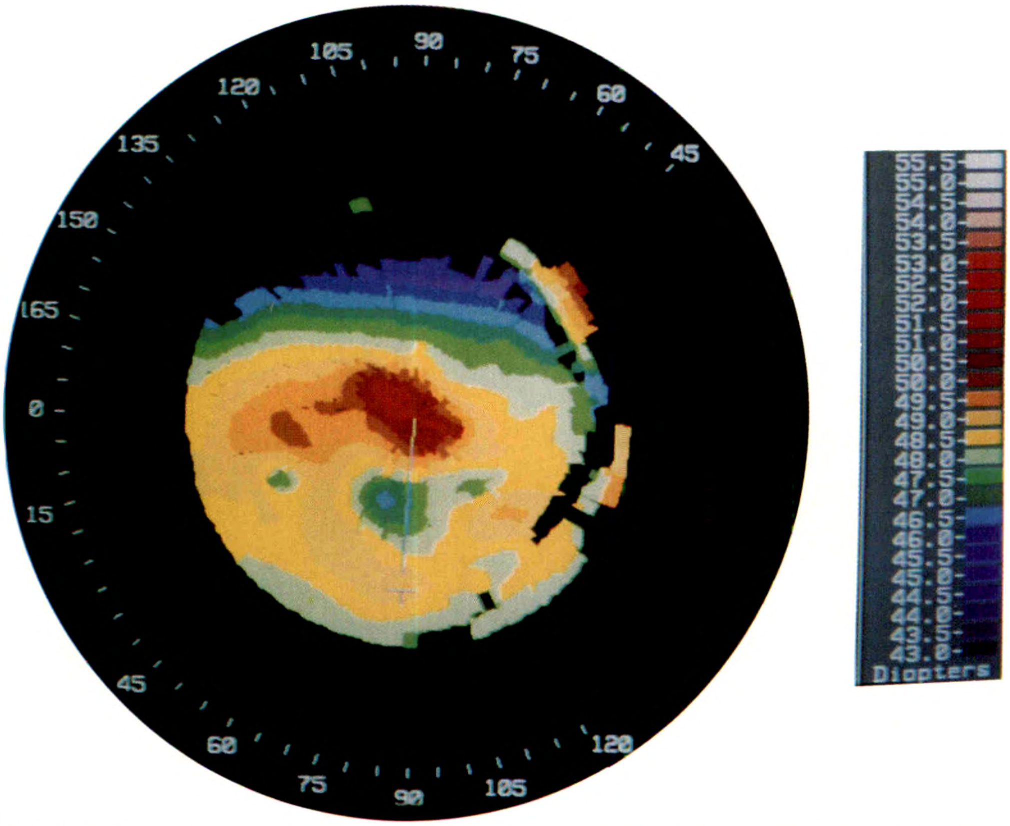


Fig. 4 (Maguire). Topographic analysis of Patient 8, who had the widest range of surface power within the central 17 rings. Each color represents a 0.5-diopter range of power. Power ranges from 45.50 to 51.50 diopters. Highest power is seen close to fixation.

that the degree of irregularity is relatively small given the high surface powers involved. They would argue that moderate degrees of irregular astigmatism after epikeratophakia for aphakia are not a cause for concern. Topographic analysis of selected patients after penetrating keratoplasty,[3] radial keratotomy,[4-6] and epikeratophakia for myopia,[1] as well as analysis of patients with conditions that produce naturally occurring astigmatism such as keratoconus[7] and pellucid marginal degeneration,[8] show that excellent spectacle-corrected visual acuity is not uncommon in patients with irregular surface topography. The epikeratophakia advocate would believe that if the patient sees well postoperatively, then the operation was a success regardless of the topographic findings.

The effect of irregular surface topography on visual performance must be better understood before judgments can be made on this or any other refractive corneal procedure. Results of contrast sensitivity studies are abnormal in many situations where irregular topography is suspected but Snellen visual acuity is normal,[9-13] including epikeratophakia for aphakia.[14,15] The problem that remains is correlating topographic findings and contrast sensitivity measurements with a patient's visual performance when confronted with the complex and varied objects encountered outside the laboratory. To address this problem, some centers are developing ray-tracing computer software that models complex scenes and displays the degree of image degradation that occurs when such objects are refracted by irregular corneal surfaces, such as those described in this study.

The results of this small study are encouraging. The degree of irregularity found in patients with good refractive results is relatively small, and the risks involved in proceeding with intraocular surgery were great. We believe that epikeratophakia will continue to be significant in the treatment of that small percentage of aphakic patients who are contact lens intolerant and at significant risk for intraocular surgery.

References

1. Maguire, L. J., Klyce, S. D., Singer, D. E., McDonald, M. B., and Kaufman, H. E.: Corneal topography in myopic patients undergoing epikeratophakia. Am. J. Ophthalmol. 103:404, 1987.
2. Gormley, D. J., Gersten, M., Koplin, R. S., and Lubkin, V.: Corneal modeling. Cornea 7:30, 1988.
3. Maguire, L. J., and Bourne, W. M.: Corneal topography of transverse keratotomies for astigmatism after penetrating keratoplasty. Am. J. Ophthalmol. 107:323, 1989.
4. Rowsey, J. J., Balyeat, H. D., Monlux, R., Holladay, J., Waring, G. O., III, and Lynn, M. J. (The PERK Study Group): Prospective evaluation of radial keratotomy. Photokeratoscope corneal topography. Ophthalmology 95:322, 1988.
5. McDonnell, P. J., McClusky, D. J., and Garbus, J. J.: Corneal topography and fluctuating visual acuity after radial keratotomy. Ophthalmology 96:665, 1989.
6. McDonnell, P. J., Garbus, J., and Lopez, P. F.: Topographic analysis and visual acuity after radial keratotomy. Am. J. Ophthalmol. 106:692, 1988.
7. Maguire, L. J., and Bourne, W. M.: Corneal topography of early keratoconus. Am. J. Ophthalmol. 108:107, 1989.
8. Maguire, L. J., Klyce, S. D., McDonald, M. B., and Kaufman, H. E.: Corneal topography of pellucid marginal degeneration. Ophthalmology 94:519, 1987.
9. Carney, L. G.: Visual loss in keratoconus. Arch. Ophthalmol. 100:1281, 1982.
10. Zadnik, K., Mannis, M. J., and Johnson, C. A.: An analysis of contrast sensitivity in identical twins with keratoconus. Cornea 3:99, 1984.
11. Mannis, M. J., Zadnik, K., and Johnson, C. A.: The effect of penetrating keratoplasty on contrast sensitivity in keratoconus. Arch. Ophthalmol. 102:1513, 1984.
12. Lin, S., Reiter, K., Dreher, A. W., Frucht-Pery, J., and Feldman, S. T.: The effect of pterygia on contrast sensitivity and glare disability. Am. J. Ophthalmol. 107:407, 1989.
13. Krasnov, M. M., Avetisov, S. E., Makashova, N. V., and Mamikonian, V. R.: The effect of radial keratotomy on contrast sensitivity. Am. J. Ophthalmol. 105:651, 1988.
14. Mannis, M. J., Zadnik, K., Johnson, C., and Adams, C.: Contrast sensitivity after epikeratophakia. Cornea 7:280, 1988.
15. Justin, N., Asbell, P. A., and Friedman, A.: Glare and contrast sensitivity testing in epikeratoplasty. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1987, p. 225.

Trabeculectomy With 5-Fluorouracil for Adult Inflammatory Glaucoma

Henry D. Jampel, M.D., Douglas A. Jabs, M.D., and Harry A. Quigley, M.D.

We reviewed the records of 12 eyes of ten adult patients with inflammatory glaucoma who underwent trabeculectomy with the adjuvant use of 5-fluorouracil between January 1986 and January 1989. Intraocular pressure decreased from 36 ± 10 mm Hg (range, 17 to 50 mm Hg) preoperatively to 11 ± 4 mm Hg (range, 3 to 17 mm Hg) postoperatively after a median follow-up of 7.75 months (range, six to 38 months). All eyes achieved an intraocular pressure of <20 mm Hg, and ten of 12 required no intraocular pressure lowering medications. The mean (± S.D.) amount of 5-fluorouracil used was 33 ± 10 mg (range, 20 to 55 mg). During the period of observation, five of 12 eyes had an episode of uveitis, but in no patient did this result in loss of intraocular pressure control. Preoperative and postoperative systemic and topical corticosteroid use was the same. Trabeculectomy with 5-fluorouracil is an effective treatment for selected cases of adult inflammatory glaucoma refractory to medical management.

SECONDARY GLAUCOMAS associated with inflammation are difficult to treat surgically. There are few published reports addressing the use of conventional filtration surgery in inflammatory glaucoma. Clinical experience suggests that the results are poor. For this reason, surgeons faced with secondary glaucomas associated with inflammation have often resorted to other procedures, such as trabeculodialysis[1,2] or cyclocryotherapy.

The use of 5-fluorouracil as an adjunct to glaucoma filtration surgery has changed the outlook for obtaining successful operations in eyes at high risk for surgical failure.[3-7] These eyes include aphakic eyes, eyes with neovascular glaucoma, and eyes with previously unsuccessful filtration operations.

The role of 5-fluorouracil in the surgical treatment of eyes with inflammatory glaucoma, however, has not been systematically examined. Weinreb[8] discussed treating five eyes with inflammatory glaucoma with trabeculectomy with 5-fluorouracil. We undertook this study to learn whether trabeculectomy with 5-fluorouracil is useful in the treatment of inflammatory glaucoma.

Material and Methods

The charts of all patients who underwent trabeculectomy for glaucoma associated with inflammation between January 1986 and January 1989 in the Glaucoma Service of the Wilmer Institute were reviewed. All eyes had documented evidence of keratic precipitates and aqueous cell and flare, and many had peripheral anterior synechiae. No eyes had pigment dispersion syndrome, exfoliation syndrome, or intraocular masses that might have been confused with inflammation. 5-Fluorouracil had been used intraoperatively and postoperatively in every patient. All surgery was performed by one of two surgeons (H.A.Q. or H.D.J.) in the following manner after informed written consent was obtained: Retrobulbar and peripheral facial blocks were given using 2% lidocaine and 0.75% bupivacaine, mixed 50:50. All surgery was performed superonasally or superotemporally. A limbal-based conjunctival flap was created starting 7 to 8 mm behind the limbus. The conjunctival incision extended for 3 to 4 clock hours. Tenectomy was performed in all patients. A 3 × 3-mm scleral flap, 2/3 of the scleral thickness, was made, and a Descemet's

Accepted for publication Oct. 18, 1989.

From the Wilmer Ophthalmological Institute, Johns Hopkins University School of Medicine, Baltimore, Maryland.

Reprint requests to Henry D. Jampel, M.D., Maumenee B-110, Johns Hopkins Hospital, 600 N. Wolfe St., Baltimore, MD 21205.

Kelly punch was used to excise approximately 1 × 2 mm of anterior chamber angle tissue. Three to five 10-0 nylon sutures were used to suture the sceral flap to the surrounding sclera. The conjunctiva was closed using a running, locking 9-0 Vicryl suture on a BV-100 needle. At the end of surgery, a subconjunctival injection of 5 mg of 5-fluorouracil in 0.5 ml of normal saline was given inferiorly through a 30-gauge needle, in addition to subconjunctival injections of dexamethasone and gentamicin.

All eyes received prednisolone acetate 1% topically every two hours while the patient was awake, and dexamethasone ointment before sleeping, starting the day after surgery. Seven to ten days after surgery, the administration of corticosteroids was decreased to four times a day, and the ointment was discontinued. The frequency of prednisolone acetate drops was then decreased by one daily dose per week. Atropine 1% sulfate drops were used in some eyes. Subconjunctival injections of 5 mg of 5-fluorouracil in 0.5 ml of normal saline were given inferiorly. The injections were discontinued when toxicity, such as a corneal epithelial defect or a conjunctival wound leak was observed, or when the appearance of the subconjunctival bleb was so favorable that further 5-fluorouracil injections were deemed unnecessary. All injections of 5-fluorouracil were given within the first ten postoperative days.

We compared the eyes receiving 5-fluorouracil to eyes of patients who underwent trabeculectomy for inflammatory glaucoma between January 1980 and December 1984, before 5-fluorouracil was used. The trabeculectomies were all performed by one surgeon (H.A.Q.). Because only three trabeculectomies for inflammatory glaucoma were performed during this period, we reviewed the charts of all patients who had cyclocryotherapy between January 1980 and August 1989 to determine if another procedure other than trabeculectomy had been performed for inflammatory glaucoma during that time.

Results

Twelve eyes of five male patients and five female patients were studied (Table 1). Five right eyes and seven left eyes were operated on. There were six white patients (six eyes) and four black patients (six eyes). One eye was aphakic, and another had undergone a previously unsuccessful trabeculectomy without 5-fluorouracil. The mean age of the patients was 46 ± 11 years (range, 33 to 72 years). The types of uveitis are listed in Table 1. In six of the eyes, there was active inflammation at the time of surgery, defined as the presence of cells or flare in the anterior chamber. 5-Fluorouracil, 33 ± 10 mg (range, 20 to 55 mg, 6.6 ± 2.0 doses) was given postoperatively.

Intraocular pressure fell from a preoperative value of 36 ± 10 mm Hg (range, 17 to 50 mm Hg) to a postoperative value of 11 ± 4 mm Hg (range, 3 to 17 mm Hg) 13.7 ± 10.3 months (range, 6 to 38 months) after surgery (Table 1). This change was statistically significant ($P < .001$, paired t-test). Postoperative intraocular pressure was measured in uninflamed eyes (except for the right eye in Patient 1). Whereas preoperatively the 12 eyes were receiving a mean of 2.9 ± 1.2 medications to lower intraocular pressure, only two eyes required drops postoperatively, with one eye receiving betaxolol 0.5%, and another receiving betaxolol 0.5% and dipivefrin 0.1% (Table 1).

Preoperative and postoperative descriptions of the appearance of the optic disk were compared, as were preoperative and postoperative visual fields. The small number of eyes and the relatively brief follow-up, however, precluded meaningful analysis.

Complications included corneal epithelial defects in five (42%) eyes, conjunctival wound leak in two (16%) eyes, and mild vitreous hemorrhage in one (8%) eye (Patient 9). None of the eyes required reoperation for increased intraocular pressure during the six to 38 months (median, 7.75 months) of follow-up. The only eye (right eye of Patient 1) that lost more than one line of Snellen visual acuity developed a dense cataract, which was consistent with the postoperative visual acuity.

Corticosteroid use, topical or systemic, was similar preoperatively and at the final postoperative visit (Figure). Three patients were taking systemic corticosteroids preoperatively and continued taking them during the follow-up period. The data do not permit a determination of whether or not systemic corticosteroids used in the perioperative period were beneficial. Five of 12 eyes had evidence of inflammation at some time in the postoperative period, but in no patient did the inflammation result in a long-term loss of intraocular pressure control.

Adequate records of 80 of 88 patients who underwent trabeculectomies between January 1980 and December 1984 were reviewed (Table

TABLE 1
PATIENT CHARACTERISTICS

			Intraocular Pressure				Visual Acuity	
Patient No., Age, Sex, Eye	Diagnosis	Level of Inflammation*	Preoperative (mm Hg)	Postoperative (mm Hg)	Epithelial Defect	Wound Leak	Preoperative	Postoperative
1, 34, M, L.E.	Idiopathic	Trace cell and flare	32	10	Present	Absent	20/40	20/30
R.E.	Idiopathic	2+ cell and flare	46	15	Present	Absent	20/200	Hand motions
2, 51, M, L.E.	Sarcoid	None	18	13	Absent	Absent	20/100	20/80
3, 33, M, L.E.	HLA B27 associated	None	30	9	Absent	Absent	20/60	20/30
4, 39, F, R.E.	Trabeculitis	None	39	9	Present	Absent	20/30	20/25
5, 51, M, L.E.	Glaucomato-cyclitic	None	17	12	Absent	Absent	20/30	20/30
6, 72, M, R.E.	Herpes simplex	1+ cell and flare	36	14	Absent	Absent	20/30	20/30
7, 53, F, R.E.	Herpes zoster	None	35	10	Present	Absent	20/30	20/40
8, 43, F, R.E.	Idiopathic	1+ cell and flare	50	15	Absent	Present	20/200	20/30
L.E.	Idiopathic	Trace cell and flare	44	8	Absent	Present	20/40	20/30
9, 57, F, L.E.	Idiopathic	1+ cell and flare	45	17	Absent	Absent	20/60	20/60
10, 37, F, L.E.	Juvenile arthritis	None	39	3	Present	Absent	20/25	20/30

*Graded on a scale of none, trace, 1+, 2+, 3+, or 4+ cell and flare at the time of surgery.

†Median, 7.75 months.

‡Because this eye had trauma that required lensectomy and vitrectomy shortly after this visit, its follow-up is shorter than for the fellow eye.

TABLE 1 *(Continued)*
PATIENT CHARACTERISTICS

INTRAOCULAR PRESSURE LOWERING MEDICATION		5-FLUOROURACIL ADMINISTERED (MG)	POSTOPERATIVE INFLAMMATION	ADDITIONAL SURGERY	LENGTH OF FOLLOW-UP (MOS)†
PREOPERATIVE	POSTOPERATIVE				
Timolol maleate 0.5%, dipivefrin hydrochloride 0.1%, acetazolamide	—	40	Flare after extracapsular cataract extraction/intraocular lens	Extracapsular cataract extraction/intraocular lens	38
Timolol maleate 0.5%, dipivefrin hydrochloride 0.1%	Betaxolol hydrochloride 1%, pilocarpine	55	Persistent	—	7.5‡
Timolol maleate 0.5%, dipivefrin hydrochloride 0.1%, methazolamide	—	20	One episode	—	29
Timolol maleate 0.5%, dipivefrin hydrochloride 0.1%, acetazolamide	—	25	—	—	26
Timolol maleate 0.5%, dipivefrin hydrochloride 0.1%, acetazolamide	—	40	—	—	12
—	—	40	One episode	—	12.5
Timolol maleate 0.5%, dipivefrin hydrochloride 0.1%, methazolamide	—	35	—	Extracapsular cataract extraction/intraocular lens	6
Timolol maleate 0.5%, acetazolamide	—	35	—	—	8
Betaxolol hydrochloride 1%, pilocarpine, acetazolamide, apraclonidine hydrochloride 1%	Betaxolol hydrochloride 1%	20	—	—	6.5
Betaxolol hydrochloride 1%, pilocarpine, apraclonidine hydrochloride 1%	—	30	One episode	—	6
Betaxolol hydrochloride 1%, dipivefrin hydrochloride 0.1%, phospholine iodide, apraclonidine hydrochloride 1%, acetazolamide	—	40	—	—	6
Timolol maleate 0.5%, dipivefrin hydrochloride 1%, pilocarpine, acetazolamide	—	20	—	—	7.5

2). In only three patients was surgery performed for glaucoma associated with inflammation. In one patient, an eye developed an intraocular pressure of 42 mm Hg and a closed internal opening six weeks after surgery. A second patient had an intraocular pressure of 22 mm Hg while taking two topical medicines two months postoperatively, and required endophotocoagulation of the ciliary processes less than one year later. The third patient had a hypotonous eye with a mature cataract three years after surgery. Review of the charts of 40 of

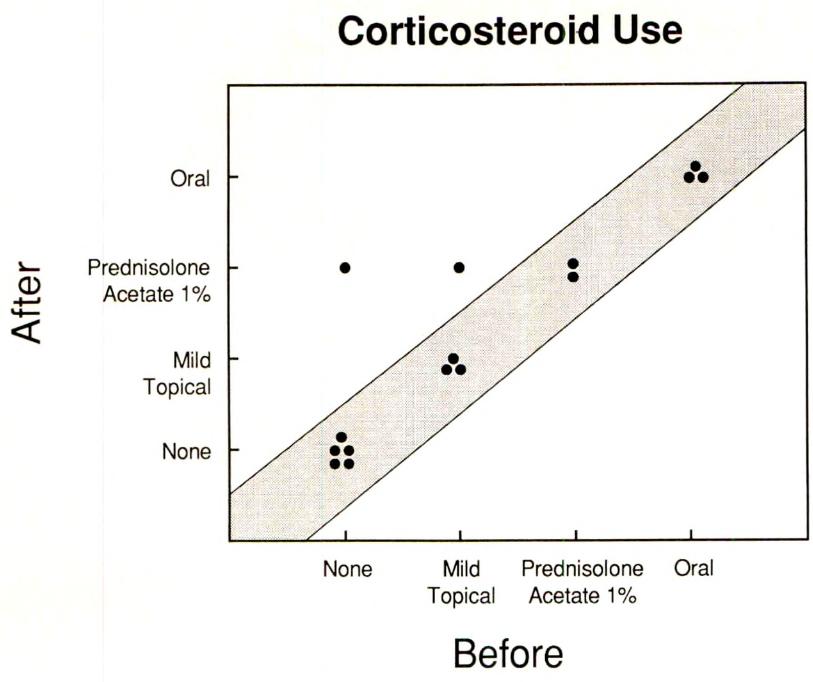


Figure (Jampel, Jabs, and Quigley). Systemic and topical corticosteroid use before and after trabeculectomy with 5-fluorouracil. Mild topical corticosteroids include fluorometholone 0.1% and 0.25%, and prednisolone acetate 0.12%. Shaded area represents equivalent preoperative and postoperative corticosteroid use. There are more points than eyes because some patients received both systemic and topical treatment.

the 45 eyes undergoing cyclocryotherapy between January 1980 and August 1989 disclosed no procedures that were performed for inflammatory glaucoma.

Discussion

We have demonstrated that trabeculectomy with 5-fluorouracil can be successful in a select group of eyes with increased intraocular pressure and inflammation. Our criteria for success of operation was based solely on intraocular pressure. Even in a study with much longer follow-up, the presence and development of cataract and cystoid macular edema might have precluded the use of visual acuity and visual field stability as a more definitive indicator of the success of the surgery.

We did not study a random sample of patients with uveitis and glaucoma. Therefore, our bias, or that of the referring ophthalmologists, could have resulted in a selection of eyes with a more favorable prognosis. For example, referring physicians might not have referred cases that they believed would have been surgical failures. Alternatively, we might have selected the procedure only for eyes that we thought had a reasonable chance of success. A review of cyclocryotherapy procedures (the procedure that would have been performed at our institution had trabeculectomy not been attempted) performed during the period of the study failed to disclose any such procedures that were performed for inflammatory glaucoma. It does not appear, therefore, that we avoided performing trabeculectomies in the most difficult cases.

Although ten of the 12 trabeculectomies with 5-fluorouracil were successful without intraocular pressure lowering medication, whereas two of three trabeculectomies that we had previously performed without 5-fluorouracil for inflammatory glaucoma were clearly failures, the small numbers preclude statistical comparison. We were unable to find a published report

TABLE 2
GLAUCOMA PROCEDURES PERFORMED

PROCEDURE	NO. OF EYES (PATIENTS)	CHARTS RETRIEVED, EYES (PATIENTS)	INFLAMMATION, EYES (PATIENTS)
Trabeculectomy			
January 1980 to December 1984	88 (73)	79 (65)	3 (3)
Cyclocryotherapy			
January 1980 to January 1989	45 (43)	40 (38)	0 (0)

of trabeculectomies without the use of 5-fluorouracil performed for inflammatory glaucoma. One might assume, however, that the success rate of trabeculectomy without 5-fluorouracil for inflammatory glaucoma would be comparable to the success rate of trabeculectomy without 5-fluorouracil in other high-risk situations such as aphakia (39% to 62%),[9,10] neovascular glaucoma (40% to 67%),[11,12] young patients (38%),[13] and eyes having undergone failed trabeculectomies (40%).[14] In this context, our results suggest that the use of 5-fluorouracil may have contributed to our high success rate.

We used a relatively low dose of 5-fluorouracil, comparable to the amounts used by Ruderman and associates[6] and Weinreb.[8] The complications observed were similar to those previously reported—epithelial defects, wound leaks, and a vitreous hemorrhage in an aphakic eye. No suprachoroidal hemorrhages occurred in our small series. Our results are similar to those of Weinreb,[8] who reported successful lowering of intraocular pressure in five of six eyes with inflammatory glaucoma after trabeculectomy with 5-fluorouracil. He suggested that the frequency and degree of uveitis were lower postoperatively than preoperatively. Our data do not lend themselves to quantitative analysis that can support or refute this observation. We did not observe any severe inflammatory exacerbations in the immediate postoperative period, nor was there any increase in the need for anti-inflammatory agents. Encouragingly, in none of the five eyes with discrete bouts of inflammation postoperatively did the operation fail as a result of the inflammation. The possibility that 5-fluorouracil might actually "treat" the uveitis remains an intriguing but unsubstantiated hypothesis.

The rationale for the use of 5-fluorouracil was that eyes with previous or active uveitis would tend to heal more quickly after surgery than eyes without uveitis. This tendency might be a result of increased permeability of the blood-aqueous barrier to mediators of inflammation and wound healing. Because our data are only suggestive, a controlled trial would be necessary to determine the precise role played by 5-fluorouracil.

References

1. Kanski, J. J., and McAllister, J. A.: Trabeculodialysis for inflammatory glaucoma in children and young adults. Ophthalmology 92:927, 1985.
2. Hoskins, H. D., Hetherington, J., and Shaffer, R.: Surgical management of the inflammatory glaucomas. Perspect. Ophthalmol. 1:173, 1977.
3. Heuer, D. K., Parrish, R. K., II, Gressel, M. G., Hodapp, E., Palmberg, P. F., and Anderson, D. R.: 5-Fluorouracil and glaucoma filtering surgery. II. A pilot study. Ophthalmology 91:384, 1984.
4. Heuer, D. K., Parrish, R. K., II, Gressel, M. G., Hodapp, E., Desjardins, D. C., Skuta, G. L., Palmberg, P. F., Navarez, J. A., and Rockwood, E. J.: 5-Fluorouracil and glaucoma filtering surgery. III. Intermediate follow-up of a pilot study. Ophthalmology 93:1537, 1986.
5. Rockwood, E. J., Parrish, R. K., Heuer, D. K., Skuta, G. L., Hodapp, E., Palmberg, P. F., Gressel, M. G., and Feuer, W.: Glaucoma filtering surgery with 5-fluorouracil. Ophthalmology 94:1071, 1987.
6. Ruderman, J. M., Welch, D. B., Smith, M. F., and Shoch, D. E.: A randomized study of 5-fluorouracil and filtration surgery. Am. J. Ophthalmol. 104:218, 1987.
7. Rabowsky, J. H., and Ruderman, J. M.: Low-dose 5-fluorouracil and glaucoma filtration surgery. Ophthalmic Surg. 20:347, 1989.
8. Weinreb, R. N.: Adjusting the dose of 5-fluorouracil after filtration surgery to minimize side effects. Ophthalmology 94:564, 1987.
9. Bellows, A. R., and Johnstone, M. A.: Surgical management of chronic glaucoma in aphakia. Ophthalmology 90:807, 1983.
10. Heuer, D. K., Gressel, M. G., Parrish, R. K., II, Anderson, D. R., Hodapp, E., and Palmberg, P. F.: Trabeculectomy in aphakic eyes. Ophthalmology 91:1045, 1984.
11. Allen, R. C., Bellows, A. R., Hutchinson, B. T., and Murphy, S. D.: Filtration surgery in the treatment of neovascular glaucoma. Ophthalmology 89:1181, 1982.
12. Parrish, R., and Herschler, J.: Eyes with end-stage neovascular glaucoma. Natural history following successful modified filtering operation. Arch. Ophthalmol. 101:745, 1983.
13. Gressel, M. G., Heuer, D. K., and Parrish, R. K.: Trabeculectomy in young patients. Ophthalmology 91:1242, 1984.
14. Schwartz, A. L., and Anderson, D. R.: Trabecular surgery. Arch. Ophthalmol. 92:134, 1974.

Comparison of Transscleral Neodymium:YAG Cyclophotocoagulation With and Without a Contact Lens in Human Autopsy Eyes

Ruthanne B. Simmons, M.D., Marino Blasini, M.D., M. Bruce Shields, M.D., and Phillip J. Erickson, M.S.

A contact lens designed to facilitate neodymium:YAG transscleral cyclophotocoagulation was evaluated on human autopsy eyes, and the lesions produced were compared to the lesions produced by similar laser treatments without a lens. Using the thermal mode at 20-msec duration, the variables studied were distance from the corneoscleral limbus (0.5, 1.5, 2.5 mm); energy (2, 4, 6, 8 J); and offset (distance between the focal points of the aiming and therapeutic beams; settings of 5, 7, 8, 9). By gross and light microscopic inspection, the ciliary body lesions produced were similar with or without the lens. A distance between 0.5 and 1.5 mm appears optimal for damaging the pars plicata. Energies of 4 to 8 J produced ciliary epithelial destruction.

Transscleral cyclophotocoagulation with a neodymium:YAG (Nd:YAG) laser is gaining popularity as an alternative cyclodestructive procedure for patients in whom conventional surgical management is inadequate. Preliminary clinical trials have supported the efficacy of this technique and have suggested possible advantages over other methods of treatment.[1-4] The most widely used technique is a noncontact method, in which the eyelids are separated manually and the laser beam is aimed through air directly at the conjunctiva.

Our early clinical experience prompted us to design a contact lens to eliminate several of the technical difficulties encountered with transscleral cyclophotocoagulation and to improve the precision of the procedure.[5] The purpose of this study was to evaluate the use of the contact lens in human autopsy eyes and to compare the gross and histologic findings to those obtained without use of a lens.

Material and Methods

The contact lens is made of polymethylmethacrylate with an antireflective coating (Fig. 1). The central portion of the lens is 12 mm in diameter with a radius of curvature of 7.45 mm, providing a shallow protective vault over the corneal epithelium. There is an 8-mm central opaque disk to protect the internal ocular structures from stray laser energy. The opaque protector is smaller than the 12-mm corneal diameter to help identify the corneoscleral limbus when aligning the contact lens.

A scleral flange extends 3 mm beyond the corneal portion of the lens. It has a constant 35-degree taper, which was found to be most effective for compressing the conjunctiva and blanching blood vessels. The estimated cone angle of the incident beam with the lens is 12 degrees.

A set of etched lines in each quadrant contains three marks placed 1 mm apart to guide placement of the laser burns. The first line is at the junction of the corneal and scleral portions of the lens and is meant to be placed at the corneoscleral limbus. The second and third etch marks are 1 and 2 mm posterior to the corneo-

Accepted for publication Nov. 13, 1989.

From the Duke University Eye Center, Durham, North Carolina (Drs. Simmons, Blasini, and Shields) and Ocular Instruments, Inc., Bellevue, Washington (Mr. Erickson). This study was presented at the annual meeting of the Association for Research in Vision and Ophthalmology, Sarasota, Florida, May 3, 1989. Mr. Erickson has a proprietary interest in the contact lens described in this study; the other authors do not.

Reprint requests to M. Bruce Shields, M.D., Duke University Eye Center, Box 3802, Durham, NC 27710.

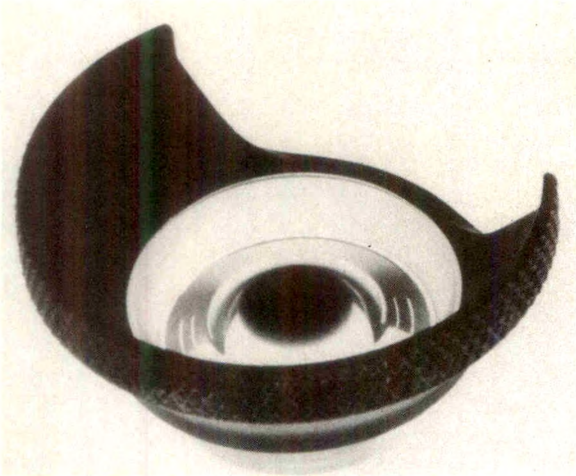


Fig. 1 (Simmons and associates). Contact lens for use with Nd:YAG cyclophotocoagulation.

scleral limbus. The edge of the lens corresponds to 3 mm posterior to the corneoscleral limbus.

A wide holding portion of the lens helps to keep the surgeon's fingers away from the laser beam and separates and protects the patient's eyelids. One quadrant of the holding portion has been removed to allow a better fit of the lens under the brow and to allow for upward rotation of the lens when visualizing the vertical quadrants.

Eighteen fresh, unpreserved, human autopsy eyes were used. The globes were placed in a Styrofoam mannequin head mounted upright in the head piece of the laser slit lamp. The globes were treated while in the primary position with reference to the laser beam, that is, a tangential approach to the sclera as opposed to a perpendicular approach was used. The Lasag Microruptor II Nd:YAG laser was used in the free-running thermal mode, using single pulses of 20-msec duration.

Three variables of laser application were studied: distance from the corneoscleral limbus; energy; and offset (distance between the focal points of the aiming and therapeutic beams). For each variable, laser applications were made first with and then without the contact lens. Saline was placed in the lens concavity, but no viscous bridge was used.

The distances studied were 0.5, 1.5, and 2.5 mm posterior to the corneoscleral limbus. The other variables were held constant at an energy of 8 J and a maximum offset of 9 (3.6 mm in air) while the distance was varied. Distance was judged using the etch marks on the contact lens. The limbal etch mark was aligned by sight with the anterior insertion of the conjunctiva in each quadrant. The laser beam was oriented approximately perpendicular to the anterior surface of the contact lens and aimed between or adjacent to the appropriate etch mark for the distance desired. Calipers were used for burns placed without a contact lens.

The energy settings studied were 2, 5, 7, and 8 J. During these experiments, the distance from the corneoscleral limbus was maintained at 1.5 mm and the offset at 9. Offsets studied were 5, 7, 8, and 9, while distance and energy were held constant at 1.5 mm and 8 J, respectively. For all three variables, adjacent laser applications were made with and without the contact lens.

After completion of the laser treatments, the eyes were sectioned at the equator and fixed for a minimum of 24 hours in acetate-buffered formaldehyde. The ciliary body was examined and photographed under a dissecting microscope. The anterior segment was then cut into wedges, each containing laser treatments of one variable performed either with or without the contact lens. Sections were prepared in the usual manner for light microscopic study. The specimens were sectioned radially (parallel to the long axis of the ciliary processes) until the areas of treatment were seen histologically.

Results

For all three variables studied, no appreciable difference was seen either under the dissecting microscope or histologically between those lesions applied using the contact lens and those applied without a lens. Disruption of the ciliary epithelium with a blister-like elevation of the epithelial layers from the underlying stroma was seen with little apparent damage to the adjacent sclera or ciliary muscle. There was evidence of pigment clumping within the cleft produced.

Lesions created with and without the lens were similarly placed in the ciliary body (Fig. 2). Lesions placed 0.5 mm posterior to the corneoscleral limbus affected primarily the peripheral iris (Fig. 3), those 1.5 mm posterior to the corneoscleral limbus affected an area just posterior to the pars plicata (Fig. 4), and those

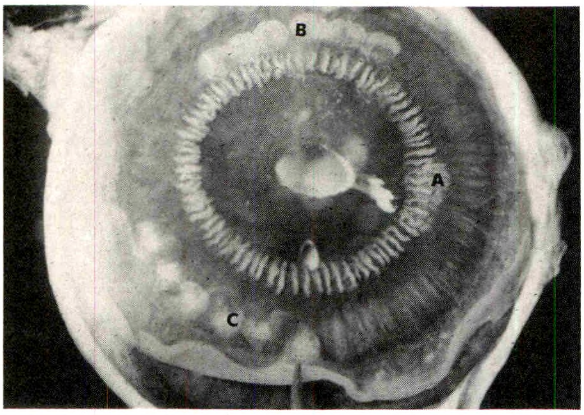


Fig. 2 (Simmons and associates). Dissecting microscopic view of human autopsy eye shows laser treatments to ciliary body with contact lens (first three lesions of each group, moving counterclockwise) and without a lens, placed 0.5 mm (A); 1.5 mm (B); and 2.5 mm (C) posterior to the corneoscleral limbus.

2.5 mm behind the corneoscleral limbus were seen in the posterior pars plana (Fig. 5).

No definite lesion was seen either grossly or histologically when an energy level of 2 J was used with or without the lens. With an energy level of 4, 6, and 8 J, the width and severity of the lesions appeared grossly to correlate with the energy level, but no difference was found histologically (Figs. 6 and 7). No difference was found between lesions created with or without the lens at these higher energy levels.

Tissue reactions were seen at all four offsets studied. The only appreciable difference was an enhanced scleral tract (an area of increased basophilic staining with slight thickening of the fibers) seen with the shorter offsets as compared with the longer offsets. The lesions were primarily in the iris or pars plana.

Discussion

The contact lens evaluated in this study was designed to facilitate certain aspects of transscleral Nd:YAG cyclophotocoagulation. Anticipated advantages of the use of the lens in this procedure include the ability to compress the conjunctiva and blanch ocular vessels; more precise placement of laser applications; and separation of the eyelids for better exposure.

Fankhauser and associates[6] used a contact lens with transscleral Nd:YAG cyclophotocoagulation. They used two different contact lenses in an attempt to vary the cone angle of the incident laser beam. One of their contact lenses produced a cone angle of 24 degrees and the other produced a cone angle of 8 degrees. (When no contact lens is used, the cone angle is 16 degrees.) They varied cone angle with offset (that is, amount of defocusing) to alter the diameter of the beam impinging on the sclera. As the cone angle increases, the depth of tissue penetration decreases, and the horizontal spread of scattered light increases. They concluded that the offset should be maximally set to decrease damage to the conjunctiva and sclera. They believed, however, that the contact lenses used had no advantage over treatment without a lens in autopsy eyes. This is consistent with our results, in which the use of a contact lens did not appear to affect the intensity or size of the lesions produced. Additionally, using a maximal offset, less scleral damage was seen histologically than with shorter offsets.

Unlike Fankhauser and associates,[6] we attempted to change the parameters of the laser beam as little as possible with our lens, because

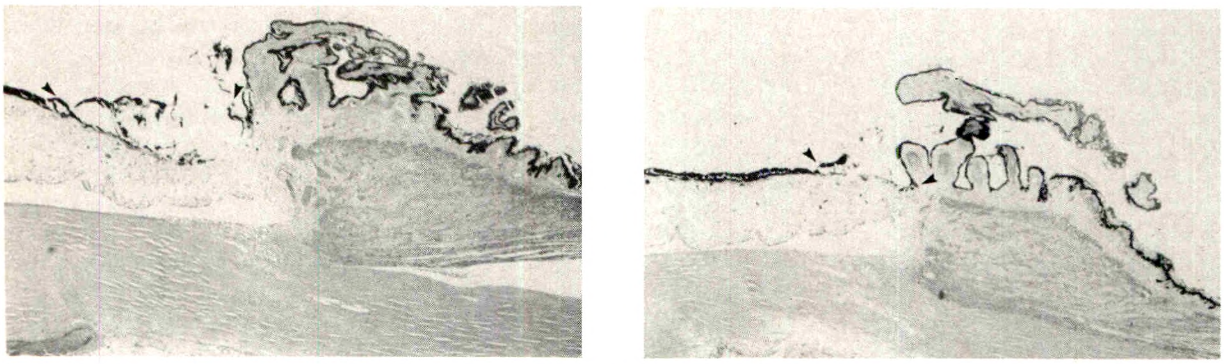


Fig. 3 (Simmons and associates). Photomicrographs of Nd:YAG laser lesions (arrows) placed 0.5 mm posterior to the corneoscleral limbus, with (left) and without (right) a contact lens. Energy setting, 8 J; offset, 9 (hematoxylin and eosin, × 67).

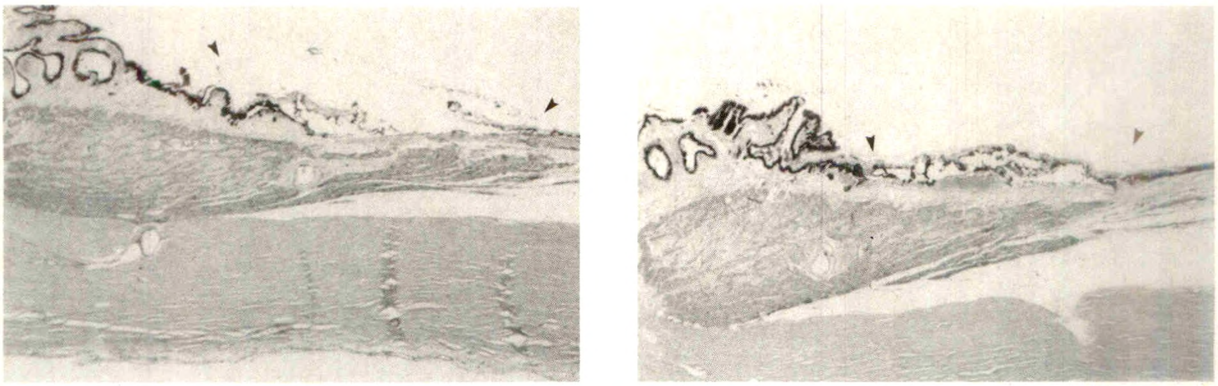


Fig. 4 (Simmons and associates). Photomicrographs of Nd:YAG laser lesions (arrows) placed 1.5 mm posterior to the corneoscleral limbus, with (left) and without (right) a contact lens. Energy setting, 8 J; offset, 9 (hematoxylin and eosin, × 67).

the purpose of the lens was to facilitate certain aspects of the clinical procedure without significantly altering the intraocular laser effects from those produced without the lens. Our results demonstrate that in human autopsy eyes the use of the contact lens does not alter the gross or histologic appearance of the laser burns applied at any parameter studied compared to the same treatment without the lens.

Our results are also consistent with those observed by Hampton and Shields[7] in human autopsy eyes. When applying the laser energy either through air or the contact lens, with the eye in primary position, a distance from the corneoscleral limbus of greater than 0.5 mm but less than 1.5 mm appeared to produce lesions closest to the peak of the pars plicata, presumably the desired area of treatment. Lesions placed at 0.5 mm posterior to the corneoscleral limbus consistently hit the peripheral iris, whereas those placed 1.5 mm posterior to the corneoscleral limbus appeared to affect primarily the posterior pars plicata or anterior pars plana. Some authors have advocated placing laser lesions as far posterior to the corneoscleral limbus as 3.0 to 6.0 mm.[8] In our study, using the tangential approach described above, lesions placed at 2.5 mm were found in the posterior pars plana. Schubert[9] found that a needle inserted 2 mm posterior to the corneoscleral limbus using a perpendicular approach or 1.5 mm posterior to the corneoscleral limbus using a para-axial approach placed the needle at the posterior margin of the corona ciliaris. Rosenberg, Ruderman, and O'Grady,[10] who used a perpendicular approach to the sclera, also found a distance of between 1.0 and 1.5 mm to be optimum for disrupting the epithelium of the ciliary processes.

It is unclear how lesions placed posterior to the pars plicata produce their pressure-lowering effect. Klapper and associates[4] reported that patients treated at 3 mm posterior to the corneoscleral limbus required less retreatment

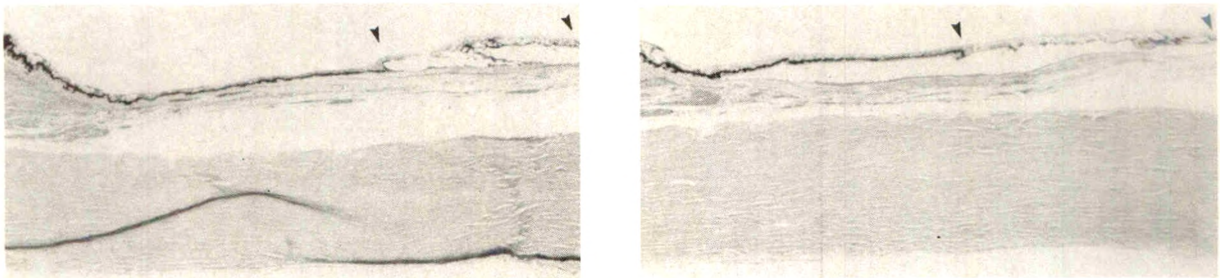


Fig. 5 (Simmons and associates). Photomicrographs of Nd:YAG laser lesions (arrows) placed 2.5 mm posterior to the corneoscleral limbus, with (left) and without (right) a contact lens. Energy setting, 8 J; offset, 9 (hematoxylin and eosin, × 67).

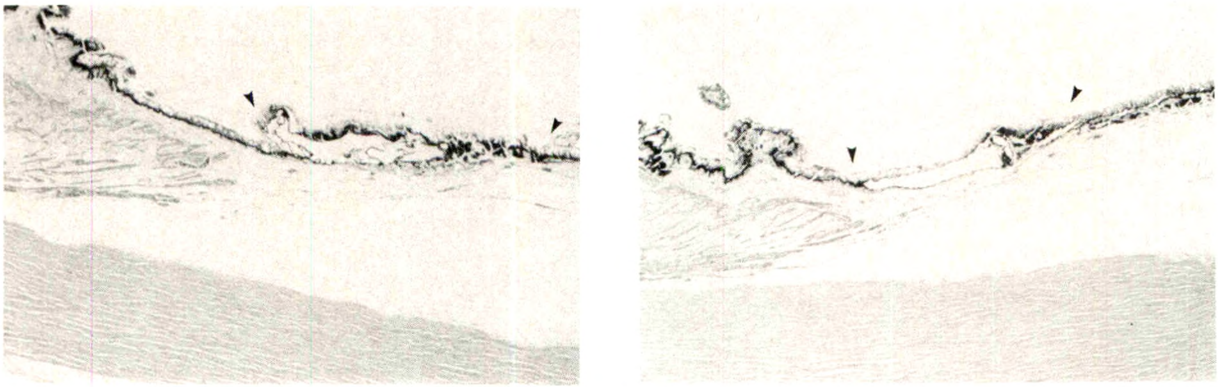


Fig. 6 (Simmons and associates). Photomicrographs of Nd:YAG laser lesions (arrows) using an energy setting of 4 J, with (left) and without (right) a contact lens. Distance from the corneoscleral limbus, 1.5 mm; offset, 9 (hematoxylin and eosin, × 67).

than patients treated 2 mm posterior to the corneoscleral limbus. More recently, however, Crymes and Gross[11] demonstrated a greater pressure-lowering effect in patients treated 1.5 mm posterior to the corneoscleral limbus compared to those treated 3.0 mm posterior to the corneoscleral limbus. Although further investigation of the pathophysiology of laser cyclodestructive procedures is clearly indicated, we believe that it is reasonable at present to continue to attempt treating the pars plicata.

Our results regarding pulse energy are consistent with those of Hampton and Shields[7] and Fankhauser and associates.[6] We found 2 J to be inadequate for producing a clearly definable histologic lesion. Energies of between 4 and 8 J consistently produced lesions, and the higher energy levels produced more severe lesions on gross examination. We continue to use 7 to 8 J in our clinical trials.

Interpretation of our findings regarding offset is difficult because most of the lesions were observed in the pars plana. Differences in offset may be more apparent when lesions are placed in the pars plicata. We believe that use of a maximal offset decreases damage to the conjunctiva and sclera and increases the intensity of the lesion, as demonstrated by previous studies.[6,7]

Although the laser lesions produced with and without the contact lens are similar in autopsy eyes, this may not be true of the living eye. In the living eye, chemosis varies the thickness of the tissues through which the Nd:YAG laser beam must pass, and conjunctival and episcleral injection increase the amount of laser energy that is absorbed at this level. Both of these features would tend to decrease the amount of laser energy reaching the ciliary processes. Fankhauser and associates[6] also commented on

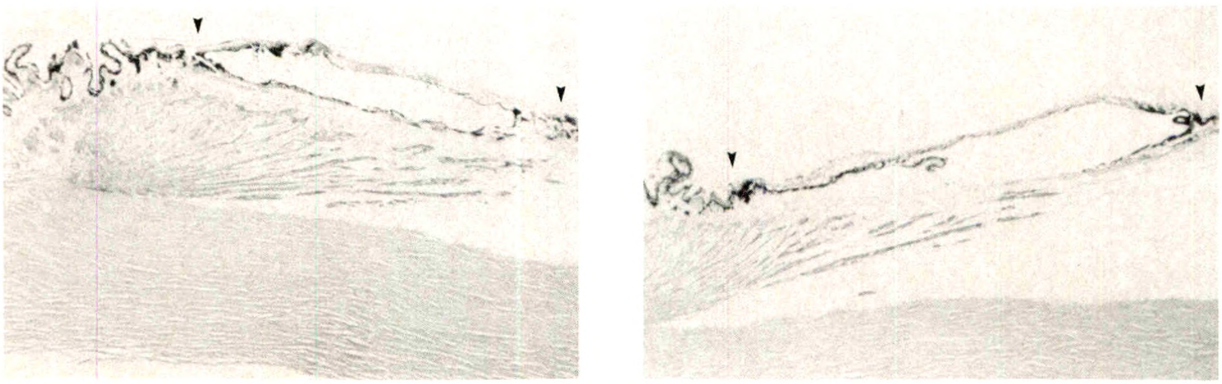


Fig. 7 (Simmons and associates). Photomicrographs of Nd:YAG laser lesions (arrows) using an energy setting of 8 J, with (left) and without (right) a contact lens. Distance from the limbus, 1.5 mm; offset, 9 (hematoxylin and eosin, × 67).

the potentially disturbing effects of a thickened conjunctiva and recommended the use of vasoconstrictors for living eyes. It is anticipated that the contact lens evaluated in this study will have the clinical advantages of compressing conjunctival tissue and blanching superficial vessels, which may increase the effect of the laser beam at the ciliary process compared to the same treatment without the lens.

References

1. Badeeb, O., Trope, G. E., and Mortimer, C.: Short-term effects of neodymium-YAG transscleral cyclocoagulation in patients with uncontrolled glaucoma. Br. J. Ophthalmol. 72:615, 1988.
2. Beckman, H., and Sugar, H. S.: Neodymium laser cyclocoagulation. Arch. Ophthalmol. 90:27, 1973.
3. Devenyi, R. G., Trope, G. E., Hunter, W. H., and Badeeb, O.: Neodymium:YAG transscleral cyclocoagulation in human eyes. Ophthalmology 94:1519, 1987.
4. Klapper, R. M., Wandel, T., Donnenfeld, E., and Perry, H. D.: Transscleral neodymium:YAG thermal cyclophotocoagulation in refractory glaucoma. A preliminary report. Ophthalmology 95:719, 1988.
5. Shields, M. B., Blasini, M., Simmons, R. B., and Erickson, P. J.: A contact lens for transscleral neodymium:YAG cyclophotocoagulation. Am. J. Ophthalmol. 108:457, 1989.
6. Fankhauser, F., van der Zypen, E., Kwasniewska, S., Rol, P., and England, C.: Transscleral cyclophotocoagulation using a neodymium YAG laser. Ophthalmic Surg. 17:94, 1986.
7. Hampton, C., and Shields, M. B.: Transscleral neodymium-YAG cyclophotocoagulation. A histologic study of human autopsy eyes. Arch. Ophthalmol. 106:1121, 1988.
8. Beckman, H., Kinoshita, A., Rota, A. N., and Sugar, H. S.: Transscleral ruby laser irradiation of the ciliary body in the treatment of intractable glaucoma. Trans. Am. Acad. Ophthalmol. Otolaryngol. 76:423, 1972.
9. Schubert, H. D.: Cyclophotocoagulation. How far posterior to the limbus is the ciliary body? Ophthalmology 96:139, 1989.
10. Rosenberg, L. F., Ruderman, J. M., and O'Grady, R. B.: Transscleral cyclophotocoagulation. Localization of ciliary process destruction. Invest. Ophthalmol. Vis. Sci. 30(suppl):353, 1989.
11. Crymes, B. M., and Gross, R. L.: The influence of laser lesion placement in neodymium:YAG cyclophotocoagulation. Invest. Ophthalmol. Vis. Sci. 30(suppl):353, 1989.

Changes in the Extracellular Matrix of the Human Optic Nerve Head in Primary Open-Angle Glaucoma

M. Rosario Hernandez, D.D.S., Wieslawa M. Andrzejewska, M.D., and Arthur H. Neufeld, Ph.D.

Using immunofluorescent staining, we were able to characterize the changes in composition and distribution of the macromolecules making up the extracellular matrix of the lamina cribrosa of the glaucomatous human optic nerve head. In tissue adjacent to the glaucomatous cups, there was marked disorganization and loss of fibers of elastin within the cores of the cribriform plates. Collagen type VI, normally sparse, increased in quantity considerably throughout the lamina cribrosa in glaucomatous eyes with all degrees of damage. Collagen type IV and other basement membrane macromolecules appeared to extend into nerve bundles, presumably filling in spaces previously occupied by nerves. There was no appreciable change in the postlaminar region, which indicates the specificity of the extracellular matrix changes in the lamina cribrosa. Our results indicate that changes in the extracellular matrix play an important role in the progression of the glaucomatous process and may be a causative agent of the disease.

PRIMARY OPEN-ANGLE GLAUCOMA is characterized by cupping of the optic nerve head attributable to progressive loss of axons and distortion of the lamina cribrosa. Quigley and associates[1,2] demonstrated that the cupping associated with glaucoma results from the compression, stretching, and rearrangement of the connective tissue plates of the lamina cribrosa in the optic nerve head in response to increased intraocular pressure. In addition to this morphologic observation, one published report[3] claimed an increase in the collagen content, and perhaps a change in collagen composition, in the lamina cribrosa of glaucomatous eyes compared to normal human eyes.

Our previous study described the extracellular matrix macromolecules that make up the connective tissue plates of the lamina cribrosa in normal human eyes.[4,5] The normal, young, human lamina cribrosa appears to have the extracellular matrix of a compliant tissue that may be resilient to acute mechanical changes such as increased intraocular pressure. In the young adult, the core of the cribriform plates supporting the axons contains elastin fibers, a network of filamentous basement membranes, and sparse fibrillar forms of collagen; the plates are coated by a basement membrane associated with astrocytes. As the lamina cribrosa ages, there is a gradual increase in fibrillar forms of collagen in the cribriform plates as well as an increase in fibers of elastin and basement membranes in the core of the plates. These changes suggest that the normal tissue may retain flexibility and resiliency with age.[6]

We used immunofluorescence to study the changes in composition and distribution of several extracellular matrix macromolecules in human optic nerve heads of eyes with primary open-angle glaucoma. We compared our findings with normal, age-matched, control human eyes.

Material and Methods

Seventeen human autopsy eyes (donor age range, 58 to 97 years) with a diagnosis of

Accepted for publication Nov. 16, 1989.

From the Ophthalmic Pharmacology Unit, Eye Research Institute and the Department of Ophthalmology, Harvard Medical School, Boston, Massachusetts. This study was supported in part by National Eye Institute research grant EY-06416, the New England Glaucoma Research Foundation, Inc. (Boston), the Glaucoma Foundation (New York), and the Foundation for Glaucoma Research (San Francisco).

Reprint requests to M. Rosario Hernandez, D.D.S., Eye Research Institute, 20 Staniford St., Boston, MA 02114.

primary open-angle glaucoma were obtained through the Foundation for Glaucoma Research, the New England Eye Bank, and the Cleveland Eye Bank. Information on the type of glaucoma and status of the disease (visual field and cup/disk ratio) was obtained by contacting the treating ophthalmologists. Eyes with diagnosis of secondary glaucoma were not included in this study. The eyes were classified as having mild, moderate, or advanced glaucoma (Table), using the information obtained from the treating ophthalmologists. Five pairs of human eyes without history of eye disease or diabetes were used as age-matching controls (donor age range, 57 to 81 years). All eyes were transported to the laboratory on ice within 24 hours after death. The interval between time of death and time of enucleation was two to six hours.

The optic nerve heads were dissected, embedded in optimum cutting temperature compound (OCT) for sagittal or cross sections, flash frozen in liquid nitrogen, and stored at −80 C until ready for study. Serial cryostat sections, 6 μm thick, of optic nerve heads were prepared and mounted on gelatin-coated slides and used for immunofluorescent staining. Serial cross sections of tissues were examined at levels adjacent, midway, and posterior in depth

TABLE

DATA OF EYES WITH THE DIAGNOSIS OF PRIMARY OPEN-ANGLE GLAUCOMA

AGE OF SUBJECT (YRS)	EYE	VISUAL FIELD*	CUP/DISK RATIO
58	R.E.	4	>0.8
58	L.E.	4	>0.8
63	R.E.	1	0.3–0.5
63	L.E.	1	0.3–0.5
69	R.E.	2	0.5–0.8
69	L.E.	2	0.5–0.8
73	L.E.	2	0.3–0.5
74	R.E.	4	>0.8
76	R.E.	NA	0.5–0.8
76	L.E.	NA	0.5–0.8
80	R.E.	2	0.3–0.5
80	L.E.	2	0.3–0.5
82	R.E.	3	0.5–0.8
82	L.E.	2	0.5–0.8
83	R.E.	3	0.5–0.8
83	L.E.	1	0.3–0.5
97	R.E.	4	>0.8

*1, no defect; 2, increasing scotoma; 3, significant defect; 4, loss of central field; NA, not available.

relative to the changing disk surface to assure views of the prelaminar region and the cribriform plates at different depths of the glaucomatous cup. Cribriform plates were also examined near the displaced central vessels and near the sclera of the glaucomatous cup.

The following antibodies were used: monoclonal antibody against human laminin (working dilution, 1:1,000), monoclonal antibody against heparan sulfate proteoglycan (working dilution, 1:25), monoclonal antibody against human collagen type IV (working dilution, 1:200), monoclonal antibody against human collagen type VI (working dilution, 1:2,000), polyclonal antibody against human collagen type I (working dilution, 1:160), polyclonal antibody against human collagen type III (working dilution, 1:50), and polyclonal antibody against pig α-elastin[7] (working dilution, 1:50).

The sections were washed three times for three minutes in phosphate-buffered saline containing 2% bovine serum albumin, covered with 35 μl of human serum diluted 1:50 in phosphate-buffered saline–bovine serum albumin, and incubated for 30 minutes. After additional washings, three times for three minutes in phosphate-buffered saline–bovine serum albumin, the sections were incubated with 35 μl of primary antibodies diluted as indicated in phosphate-buffered saline–bovine serum albumin for 30 minutes at room temperature, washed three times for three minutes in phosphate-buffered saline–bovine serum albumin, and incubated for 30 minutes at room temperature with the appropriate rhodamine-conjugated second antibody (working dilution, 1:16). After the incubation, the slides were washed three times for three minutes in phosphate-buffered saline–bovine serum albumin and mounted in 1:5 glycerol-phosphate buffered saline.

The specificity of the antisera was demonstrated by replacing the primary antibody with antibody that was preabsorbed with the appropriate purified antigen. In additional controls, the first antibody was omitted and replaced by nonimmune human serum followed by the second fluorescent antibody. To check for autofluorescence of the tissue, the first and second antibodies were omitted.

The slides were observed and photographed with a microscope equipped with epifluorescent illumination and appropriate filter systems. The exposure time was set automatically.

Results

As previously reported, in the prelaminar region of normal human eyes the extracellular matrix was found only around blood vessels.[4,5] Collagen type IV, laminin, and heparan sulfate localized to the vascular basement membrane. The age-related increase in the thickness of basement membrane material around blood vessels in the prelaminar region was evident in the normal eyes used as controls in this study.[6] Interstitial collagen types I, III, and VI were also present in the blood vessel walls. Elastin was only present in larger vessels.

In primary open-angle glaucoma, basement membrane material surrounded blood vessels and extended between the nerve bundles. This material occupied a greater area with the progression of the disease (Fig. 1). In sagittal sections of optic nerve heads with advanced cupping, the compressed prelaminar region was filled with basement membrane material in addition to that associated with blood vessels (Fig. 1).

In normal eyes, the basement membrane components collagen type IV, laminin, and heparan sulfate appeared as linear irregular coatings of the cribriform plates. Inside the core of the cribriform plates, basement membranes formed a network of filamentous material demonstrated in Figure 2 by the staining for collagen type IV. In the lamina cribrosa of glaucomatous eyes, there was a marked increase in the density of the collagen type IV filamentous material inside the core of the cribriform plates. In cribriform plates adjacent to the disk surface, basement membranes extended into the nerve bundles, presumably taking up space formerly occupied by nerves (Fig. 2). The vascular basement membranes throughout the lamina cribrosa did not show any changes associated specifically with glaucoma.

Elastin was present as longitudinal fibers within the core of the cribriform plates in normal eyes (Fig. 3). In glaucomatous eyes in regions immediately adjacent to the disk surface, there was disorganization and a marked loss of fibers of elastin in the cores of the cribriform plates. These changes may be progressive between moderate and advanced primary open-angle glaucoma. In regions near the central vessels or in the periphery of the lamina cribrosa near the sclera, the glaucomatous cribriform plates contained normal-appearing elastin fibers and abundant masses of granular α-elastin. In posterior cross-sectional views of the lamina cribrosa at the level of the floor of the glaucomatous cup, the bundles of fibers of elastin appeared more compact, indicating compression of the tissue.

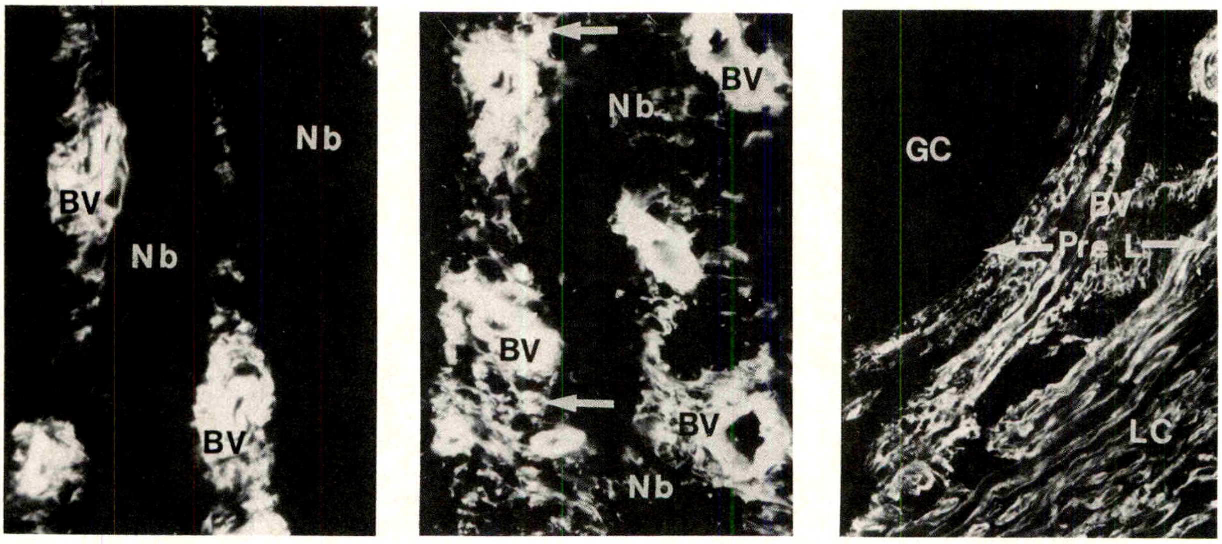


Fig. 1 (Hernandez, Andrzejewska, and Neufeld). Immunofluorescent staining for collagen type IV in sagittal sections of the prelaminar region of the human optic nerve head. Left, Normal, 72-year-old patient (×450). Middle, Mild primary open-angle glaucoma, 63-year-old patient. Note the increased presence of collagen type IV associated with blood vessels (BV) and between nerve bundles (Nb) (arrows) (×450). Right, Advanced primary open-angle glaucoma, 74-year-old patient. At a lower magnification (×225), the compressed prelaminar region (PreL) is filled with basement membranes. LC, lamina cribrosa; GC, glaucomatous cup.

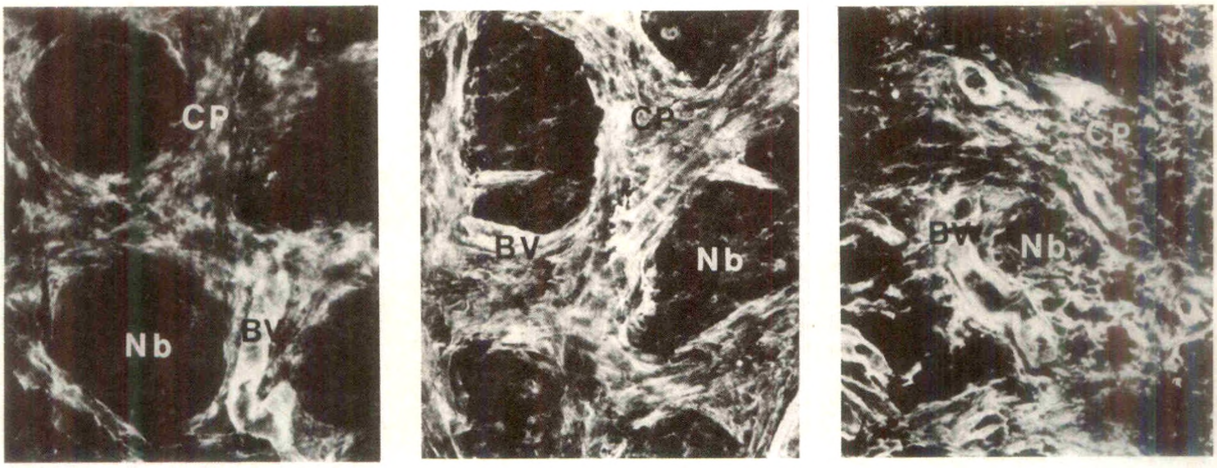


Fig. 2 (Hernandez, Andrzejewska, and Neufeld). Immunofluorescent staining for collagen type IV in cross sections of the lamina cribrosa of the human optic nerve head (× 450). Left, Normal, 75-year-old patient. Note blood vessel (BV). Middle, Moderate primary open-angle glaucoma, 82-year-old patient. Note the increase in collagen type IV material inside the core of the cribriform plates (CP). Right, Advanced primary open-angle glaucoma, 58-year-old patient. Basement membranes extend from the cribriform plates into the nerve bundles (Nb).

Collagen type VI in normal eyes appeared as a discontinuous linear layer at the edge of the cribriform plates and as sparse patches of staining inside the core (Fig. 4). Blood vessels were also positively stained. In glaucoma, staining for collagen type VI was considerably more intense, and the patchy material within the cores increased in quantity (Fig. 4). The increase in the density of collagen type VI in glaucoma was evident throughout the lamina cribrosa and was present in glaucomatous eyes with all degrees of damage.

As previously reported,[5,6,8] collagen type I was present as fibers inside the core of the cribriform plates (Fig. 5). In glaucomatous eyes with mild-to-moderate damage, there was no change in the pattern of staining except for the normal age-related increase. In advanced glaucoma, bundles of fibers of collagen type I appeared more compact within the same plate, in sections at the level of the floor of the glaucomatous cup (Fig. 5).

Collagen type III and fibronectin did not show any significant changes in glaucomatous tissues.

The only change observed in the pial septa of glaucomatous eyes was the increase in area of extracellular matrix attributable to the enlargement of the septa as a consequence of loss of neural tissue. As shown in Figure 6, collagen type IV was present in the basement membranes lining the septa. The characteristics of the basement membrane were similar in both normal and glaucomatous eyes and showed the normal age-related increase in thickness previously described in this age group.[6] Collagen type VI was present at the edge of the septa in normal eyes and unlike in the lamina cribrosa, this pattern did not change in glaucoma (Fig. 6). Other extracellular matrix components did not show major changes in the pial septa of glaucomatous eyes.

Discussion

In this study, using immunofluorescence, we examined the extracellular matrix components of the optic nerve head from eyes with the diagnosis of primary open-angle glaucoma and from age-matched normal eyes. Combining sagittal views and serial cross sections, we were able to visualize the changes in the extracellular matrix in the different levels and regions of the glaucomatous optic nerve head. Sections at the level of the floor of the cup disclosed the effect of compression of the extracellular matrix of the cribriform plates. Examination of the region of the lamina cribrosa made up of the remnant cribriform plates adjacent to the disk surface, where the pores appeared oval-shaped or elongated,[9] showed the effect of stretching on the extracellular matrix.

We observed an increase in the density and area occupied by basement membranes in the

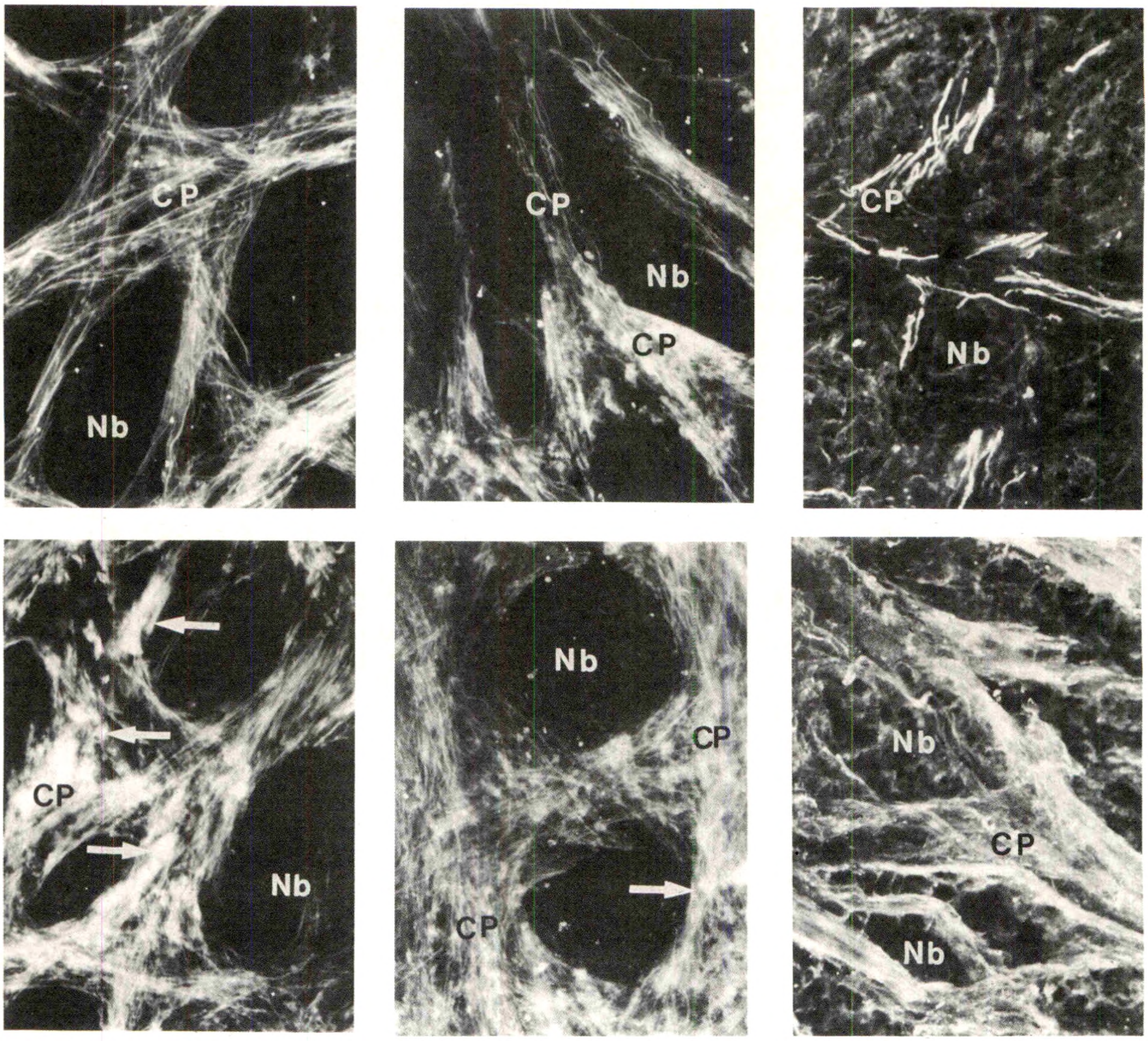


Fig. 3 (Hernandez, Andrzejewska, and Neufeld). Immunofluorescent staining of α-elastin in cross section of the lamina cribrosa (× 450). Top left, Normal, 70-year-old patient, cribriform plate (CP), nerve bundle (Nb). Top middle, Moderate primary open-angle glaucoma, 69-year-old patient. In a region adjacent to the surface of the disk, note the gradual loss of fibers of elastin. Top right, Advanced primary open-angle glaucoma, 58-year-old patient. In a region adjacent to the disk surface, note the disorganization and loss of fibers of elastin in remaining cribriform plates. Bottom left, Mild primary open-angle glaucoma, 73-year-old patient. Note the presence of granular deposits (arrows) in addition to the fibers of elastin in core of the cribriform plates in the peripheral lamina cribrosa near the sclera. Bottom middle, Advanced primary open-angle glaucoma, 58-year-old patient. In cribriform plates around the displaced central vessels, note the marked increase in granular material; the fibers of elastin are barely visible. Bottom right, Moderate primary open-angle glaucoma, 69-year-old patient. Cross section at the level of the floor of the glaucomatous cup. Note that the bundles of fibers of elastin appear more compact.

prelaminar region and in the lamina cribrosa of human glaucomatous eyes. A similar observation was recently reported in experimental glaucoma in primates.[10] Histopathologic examination of glaucomatous human eyes in early or moderate stages of injury demonstrated glial hyperplasia in both the laminar and prelaminar regions.[11] These proliferating glial cells are the most likely source of newly synthesized basement membranes and probably represent a response to injury and the loss of axons during the glaucomatous process.

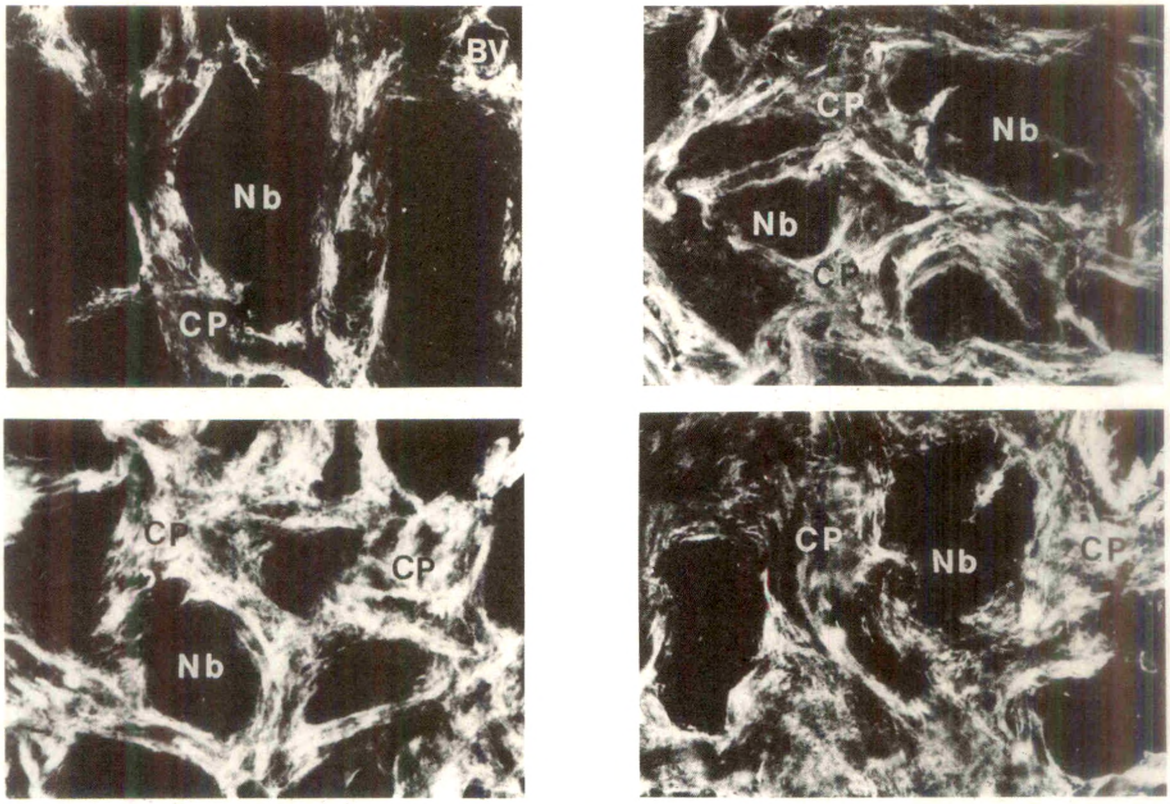


Fig. 4 (Hernandez, Andrzejewska, and Neufeld). Immunofluorescent staining for collagen type VI in cross sections of the lamina cribrosa (×450). Top left, Normal, 81-year-old patient. Collagen type VI is present at the edge of the cribriform plates (CP) and inside the core as patches of staining nerve bundle (Nb). Top right, Mild primary open-angle glaucoma, 73-year-old patient. Note the increase in collagen type VI in the cribriform plates of the peripheral lamina cribrosa near the sclera. Bottom left, Moderate primary open-angle glaucoma, 82-year-old patient. In a region next to the central vessels note the progressive increase in collagen type VI. Bottom right, Advanced primary open-angle glaucoma, 58-year-old patient. In a section of floor of the glaucomatous cup, the cribriform plates contain marked amounts of collagen type VI.

In a variety of diseases, fibers of elastin appear as globular amorphous masses or fragmented fibers.[12-14] These changes may be attributable to abnormal degradation, elastolytic degeneration, or altered biosynthesis of elastin and may underlie loss of elasticity of the organ. In the cribriform plates of the glaucomatous lamina cribrosa, granular masses of elastin appear and the fibers of elastin are increasingly disorganized with the progression of the disease. In severe primary open-angle glaucoma, there is marked loss of elastin from the cribriform plates immediately bordering the disk surface. Using laser Doppler velocimetry, Zeimer and Ogura[15] recently reported that optic nerve head compliance diminishes as the glaucomatous damage progresses. The changes in the elastin fiber organization and decreases in density of elastin fibers that we observed in the lamina cribrosa may explain the loss of compliance of the optic nerve head in primary open-angle glaucoma.

Collagen type VI forms a filamentous network in the extracellular matrix. This form of collagen is found in most tissues between and connecting fibers of collagen types I and III and near basement membranes.[16] In the normal lamina cribrosa, collagen type VI is localized at the edge, and as patches of staining in the core, of the cribriform plates. In glaucoma, collagen type VI increases markedly in amount and density, especially in the core of the plates. The increase in collagen type VI is apparent at all stages of the glaucomatous process and throughout the entire lamina cribrosa, suggesting that collagen type VI may be a reactional form of collagen in this tissue. Although little is known about the physiologic properties of this

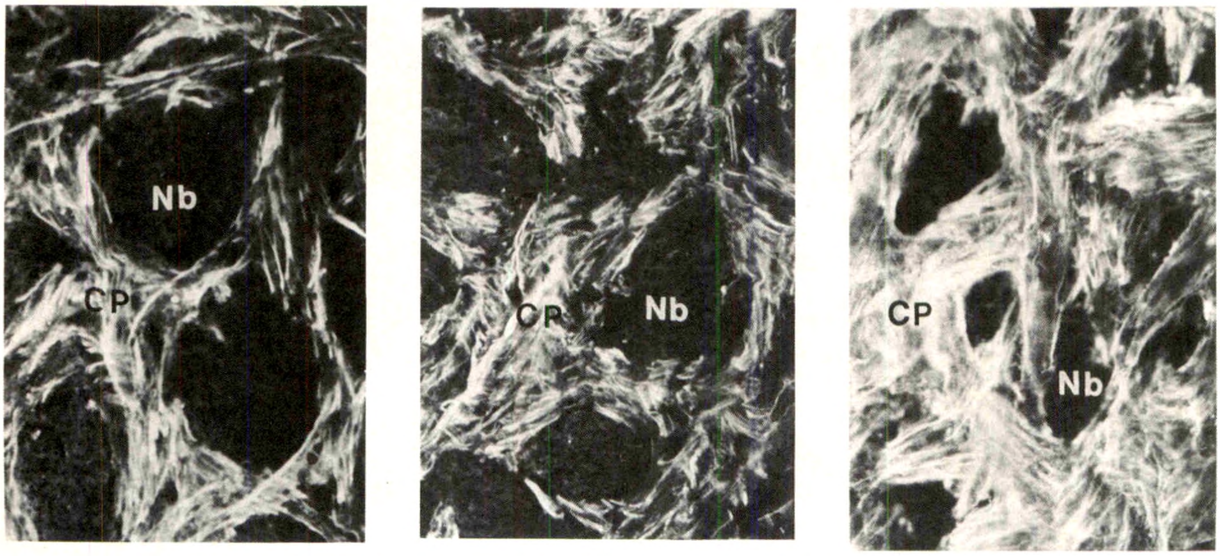


Fig. 5 (Hernandez, Andrzejewska, and Neufeld). Immunofluorescent staining for collagen type I in cross sections of the human lamina cribrosa (×450). Left, Normal, 61-year-old patient. Middle, Moderate primary open-angle glaucoma, 76-year-old patient. In a region adjacent to the disk surface, note that collagen type I occupies a larger area when compared to a normal patient but the pattern of staining does not change. Right, Advanced primary open-angle glaucoma, 58-year-old patient. Cross section of the lamina cribrosa at the level of the floor of the glaucomatous cup. Note the marked increase in apparent density of collagen type I.

collagen type, its three-dimensional structure as an open irregular network of branching filaments between collagen fibers and other microfibrils indicates a role in the maintenance of the superstructure of the extracellular matrix.[17,18] The marked increase of collagen type VI in glaucoma may represent an attempt of the tissue to maintain a failing structure.

Changes noted with immunofluorescent histochemical techniques may be caused by synthesis or degradation of specific components of the extracellular matrix, or caused by exposure of more or less antigenic sites attributable to nonspecific changes in other macromolecular components. The dramatic loss of elastin staining as fibers and the accumulation of specifically stained amorphous granular material is probably caused by degradation and reorganization of elastin in the glaucomatous cup. The increase in collagen type VI may be attributable to synthesis of this macromolecule or loss of other components from the extracellular matrix, making collagen type VI more visible with immunofluorescent staining.

Collagen type I, normally present in the core of the cribriform plates,[5,6,8] apparently does not change in amount or density in eyes with mild or moderate damage, except for the increase attributable to the larger area occupied by extracellular matrix. In advanced primary open-angle glaucoma, collagen type I increases in density, and bundles of fibers appear thicker or ribbon-like, probably because of the severe compression of the remaining cribriform plates forming the floor of the cup.

Interestingly, the extracellular matrix of the pial septa does not show changes in primary open-angle glaucoma except for the increase in amount because of the larger area of the septa. This further underscores the site of the pathogenesis of this disease as the lamina cribrosa and the specificity of the extracellular matrix changes in this tissue. Study of the changes in the extracellular matrix in secondary glaucoma, low-tension glaucoma, and other optic nerve degenerations would provide further important information.

Our previous study[6] showed that with age the extracellular matrix of the normal lamina cribrosa becomes more dense but remains organized as the area of connective tissue increases. In the glaucomatous lamina cribrosa, there are marked changes in the organization and amounts of extracellular matrix macromolecules. The changes in the cribriform plates bordering the disk surface in mildly and moderately glaucomatous eyes may represent a reaction of the tissue to stretching. These changes

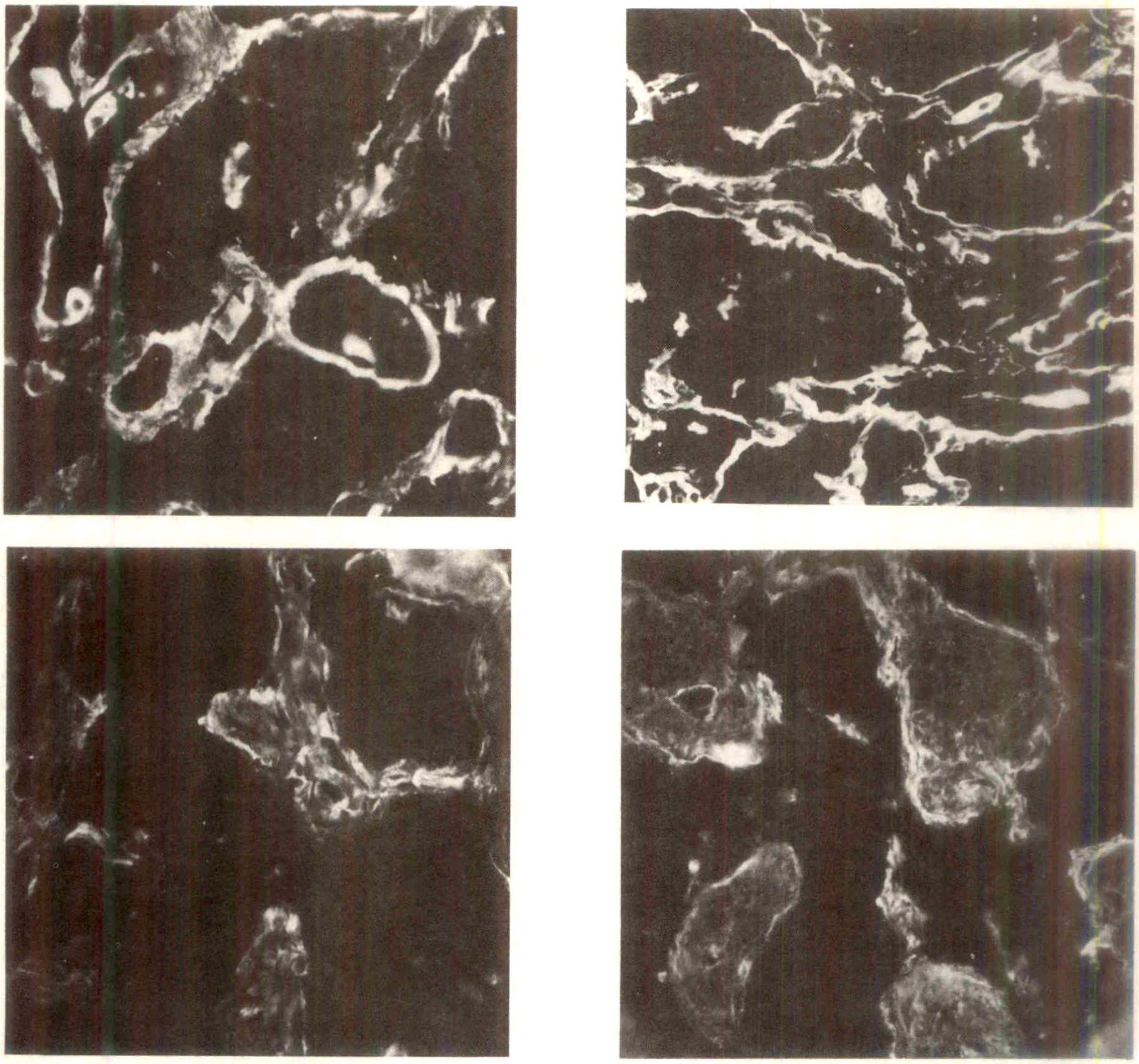


Fig. 6 (Hernandez, Andrzejewska, and Neufeld). Immunofluorescent staining for collagen types IV (top) and VI (bottom) of the postlaminar optic nerve (× 450). Top left, Normal, 88-year-old patient. Pial septa are lined by basement membranes. Top right, Advanced primary open-angle glaucoma, 58-year-old patient. The septa occupy a larger area. Bottom left, Normal, 88-year-old patient. Bottom right, Advanced primary open-angle glaucoma, 87-year-old patient. Collagen type VI localizes at the edges and as a diffuse staining in the core of the septa. No difference between normal and primary open-angle glaucoma can be observed.

include increases in collagen type IV and VI and both disorganization and loss of elastic fibers. The glaucomatous changes, as observed in sections of the floor of the cup, may represent the compression of the tissue and appear at the light microscopic level as compact bundles of collagen and elastin fibers. Whether these changes are the response to the loss of neural tissue and subsequent rearrangement of the cribriform plates because of increased intraocular pressure, or imply a predisposing weakness in this connective tissue in individuals who cannot withstand increased intraocular pressure, remains to be determined.

Acknowledgments

Jeffrey Davidson, M.D., Vanderbilt University, provided the antibody against pig α-elastin, and Eva Engvall, Ph.D., La Jolla Research Foundation, provided the monoclonal antibody against human collagen type VI.

References

1. Quigley, H. A., and Addicks, E. M.: Regional differences in the structure of the lamina cribrosa and their relation to glaucomatous optic nerve damage. Arch. Ophthalmol. 99:137, 1981.

2. Quigley, H. A., Hohman, R. M., Addicks, E. M., Massof, R. W., and Green, W. R.: Morphologic changes in the lamina cribrosa correlated with neural loss in open-angle glaucoma. Am. J. Ophthalmol. 95:673, 1983.

3. Tengroth, B., and Ammitzboll, T.: Changes in the content and composition of collagen in the glaucomatous eye. Basis for a new hypothesis for the genesis of chronic open angle glaucoma. Acta Ophthalmologica 62:999, 1984.

4. Hernandez, M. R., Igoe, F., and Neufeld, A. H.: Extracellular matrix of the human optic nerve head. Am. J. Ophthalmol. 102:139, 1986.

5. Hernandez, M. R., Luo, X. X., Igoe, F., and Neufeld, A. H.: Extracellular matrix of the human lamina cribrosa. Am. J. Ophthalmol. 104:567, 1987.

6. Hernandez, M. R., Luo, X. X., Andrzejewska, W., and Neufeld, A. H.: Age-related changes in the extracellular matrix of the human optic nerve head. Am. J. Ophthalmol. 107:476, 1989.

7. Giro, M. G., Hill, K. E., Sanberg, L. B., and Davidson, J. M.: Quantitation of elastin production in cultured vascular smooth muscle cells by a sensitive and specific enzyme-linked immunoassay. Coll. Relat. Res. 4:21, 1984.

8. Anderson, D. A.: Ultrastructure of human and monkey lamina cribrosa and optic nerve head. Arch. Ophthalmol. 82:800, 1969.

9. Miller, K. M., and Quigley, H. A.: The clinical appearance of the lamina cribrosa as a function of the extent of glaucomatous optic nerve damage. Ophthalmology 95:135, 1988.

10. Morrison, J., Dorman, M. E., and Quigley, H.: Extracellular matrix changes in glaucomatous optic atrophy. ARVO Abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1989, p. 201.

11. Minckler, D. S., and Spaeth, G. L.: Optic nerve damage in glaucoma. Surv. Ophthalmol. 26:128, 1981.

12. Kitano, Y., Nishida, K., Okada, N., Mimaki, T., and Yabuuchi, H.: Cutis laxa with ultrastructural abnormalities of elastic fiber. J. Am. Acad. Dermatol. 21:378, 1989.

13. Uchiyama, S., and Fukuda, Y.: Abnormal elastic fibers in elastosis of breast carcinoma. Acta Pathol. Jpn. 39:245, 1989.

14. Fukuda, Y., Masuda, Y., Ishizaki, M., Masugi, Y., and Ferrans, V. J.: Morphogenesis of abnormal elastic fibers in lungs of patients with panacinar and centriacinar emphysema. Hum. Pathol. 20:652, 1989.

15. Zeimer, R. C., and Ogura, Y.: The relation between glaucomatous damage and optic nerve head mechanical compliance. Arch. Ophthalmol. 107:1232, 1989.

16. Keene, D. R., Engvall, E., and Glanville, R. W.: Ultrastructure of type VI collagen in human skin and cartilage suggests an anchoring function for this filamentous network. J. Cell. Biol. 107:1995, 1988.

17. Bruns, R. R., Press, W., Engvall, E., Timpl, R., and Gross, J.: Type VI collagen in extracellular, 100-nm periodic filaments and fibrils. Identification by immunoelectron microscopy. J. Cell. Biol. 103:393, 1986.

18. Engvall, E., Hessle, H., and Klier, G.: Molecular assembly, secretion and matrix deposition of type VI collagen. J. Cell. Biol. 102:703, 1986.

OPHTHALMIC MINIATURE

The blind always come as such a surprise,
suddenly filling an elevator
with a great white porcupine of canes

Ted Kooser, *The Blind Always Come as Such a Surprise*
In Jon Mukand, editor: *Sutured Words: Contemporary Poetry About Medicine*
Brookline, Mass., Aviva Press, 1987, p. 313

Effects and Interactions of Epinephrine, Norepinephrine, Timolol, and Betaxolol on Outflow Facility in the Cynomolgus Monkey

James C. Robinson, M.D., and Paul L. Kaufman, M.D.

Total outflow facility was determined in cynomolgus monkeys by two-level constant pressure perfusion. Topical epinephrine increased facility by 30% to 35% three to four hours after dosing, whether given as a single 600-µg dose or as twice daily 600-µg doses for three days. A single 5.5-µg intracameral dose of epinephrine or norepinephrine increased facility by 65% to 70% three to four hours after dosing. A single 180-µg topical dose of timolol or betaxolol had no effect on facility three to four hours later. Timolol pretreatment prevented the facility-increasing effect of both topical epinephrine and intracameral norepinephrine, but betaxolol pretreatment prevented neither. These findings indicate that no cumulative facility-increasing effect of epinephrine, beyond the acute (three hour) facility-increasing effect, develops within three days; there may be a facility-decreasing effect of large topical epinephrine doses on the vascular structures external to the trabecular meshwork; there is no, or only subthreshold, facility-affecting ambient β-adrenergic tone in the meshwork; and the facility-increasing effect of both epinephrine and norepinephrine is mediated by β_2-adrenergic receptors in the trabecular endothelium.

Certain catecholamines administered topically or intracamerally increase outflow facility in human and monkey eyes.[1-7] Physiologic and biochemical evidence indicates that the facility increase is mediated by β-adrenergic receptors, presumably of the β_2 subtype, in the trabecular endothelium.[5,6,8,9] In humans, it has been reported that the facility-increasing effect of topical epinephrine may be greater after multiple treatments over a period of time than after a single dose.[10]

Beta-adrenergic antagonists are used in the treatment of glaucoma. These agents act by decreasing the rate of aqueous humor formation.[11-13] Timolol, a nonselective β_1-β_2-adrenergic antagonist, and betaxolol, a relatively selective β_1-adrenergic antagonist, do not affect outflow facility in humans.[11,14,15]

The interactions of timolol and betaxolol with epinephrine in relation to aqueous outflow are clinically important in glaucoma therapy, but the existing information is sparse and contradictory.[12,14,16] Several clinical studies have shown that pretreatment with timolol prevented the facility-increasing effect of epinephrine given subsequently.[12,16] Betaxolol given before epinephrine, however, did not prevent the facility-increasing effect.[14] This difference was attributed to blockade of β_2-adrenergic receptors in the trabecular endothelial cells by timolol but not by betaxolol.

The aqueous drainage system of the cynomolgus monkey (*Macaca fascicularis*) and its outflow facility responses to epinephrine and norepinephrine[4-6] are similar to that of the human.[12,14,16] Because the cynomolgus monkey is the most frequently used subhuman primate for studies of aqueous dynamics; the human data about the interactions of timolol and betaxolol with epinephrine are confusing; and the monkey allows more precise measurements under more controlled conditions than is possible in the human, we decided to study these interactions in the cynomolgus monkey.

We studied the outflow facility effects of the following: single doses of topical and intracam-

Accepted for publication Nov. 28, 1989.
From the Department of Ophthalmology, University of Wisconsin School of Medicine, Madison, Wisconsin.
This study was supported by National Eye Institute grant EY02698.
Reprint requests to Paul L. Kaufman, M.D., Department of Ophthalmology, University of Wisconsin, Clinical Science Center, 600 Highland Ave., Madison, WI 53792.

eral epinephrine and intracameral norepinephrine; multiple topical doses of epinephrine; single topical doses of timolol and betaxolol; and timolol or betaxolol given before epinephrine or norepinephrine.

Material and Methods

Eighteen young adult female cynomolgus monkeys weighing 2.0 to 3.8 kg were used. All perfusions were performed after an intramuscular injection of 10 mg/kg of body weight of ketamine followed by an intramuscular injection of 35 mg/kg of body weight of pentobarbital sodium.

Total outflow facility was determined by two-level constant pressure (2.5 and 11.9 mm Hg above naturally occurring intraocular pressure) perfusion of the anterior chamber with artificial aqueous humor,[17] using a one-needle technique and correcting for the internal resistance of the perfusion apparatus.[17,18] Eyes were studied only when the anterior chamber was free of cell and flare biomicroscopically; four to eight weeks elapsed between perfusions.

For intracameral dosing, l-epinephrine bitartrate and l-norepinephrine bitartrate were dissolved in artificial aqueous humor. The pH of the solutions was adjusted by adding NaOH so that after tenfold dilution of the fluid in the anterior chamber, the pH would be between 7.1 and 7.4. The dose for both drugs was 10 μg of the bitartrate salt (equivalent to 5.5 μg of epinephrine free-base) in 10 μl of artificial aqueous humor. In previous studies,[4,5] this dose produced consistent and significant facility increases in cynomolgus monkeys.

The drug was administered to one eye of the anesthetized animal by means of a 26-gauge needle, which was shot transcorneally into the anterior chamber with a needle gun and connected, by means of polyethylene tubing, to a micrometer syringe; the opposite eye similarly received an equal volume of artificial aqueous humor without drug. The needles were left in place without additional fluid infusion, and the animal was undisturbed for the next three hours.

All topical drugs were administered as two 5-μl drops, 30 seconds apart, to the central cornea of the fully conscious, manually restrained monkey. Blinking was prevented between drops and for 30 seconds after the last drop, and the eyelids were then wiped dry. These measures were designed to minimize the risk of systemic and local drug transfer to the untreated eye.[19,20]

Crystalline epinephrine bitartrate, 800 mg, was added to the contents of a full bottle of commercial ophthalmic epinephrine hydrochloride, which created a solution containing epinephrine hydrochloride and epinephrine bitartrate equivalent to 6.0% epinephrine free-base.[21] The topical dose was thus 600 μg/treatment.

Crystalline betaxolol hydrochloride, 100 mg, was added to 5 ml of 0.5% betaxolol hydrochloride, which created a solution concentration of 1.8% betaxolol. The dose for all experiments was 180 μg.

Crystalline timolol maleate, 100 mg, was added to 5 ml of 0.5% timolol maleate for a final concentration of 1.8% timolol. The dose for all experiments was 180 μg.[21]

The doses for all experiments involving topical epinephrine, timolol, and betaxolol were chosen because they approximate the doses used clinically in humans: 500 to 1,000 μg of epinephrine (one 50-μl drop of a 1% or 2% solution), 75 to 150 μg of timolol (one 30-μl drop of a 0.25% or 0.5% solution), and 150 μg of betaxolol (one 30-μl drop of a 0.5% solution).

Topical epinephrine (eight monkeys), timolol (six monkeys), or betaxolol (six monkeys) was given randomly to one eye of the anesthetized animal, with the opposite eye receiving an equal volume of artificial aqueous humor. The animal was then observed for the next three hours. Each eye was then cannulated with a branched needle, 15 minutes was allowed for stabilization, and total outflow facility was determined for 45 minutes thereafter.

Intracameral epinephrine (eight monkeys) or norepinephrine (nine monkeys) was administered to one eye of the anesthetized animal, with the opposite eye receiving an equal volume of artificial aqueous humor. Three hours later, each eye was cannulated with a branched needle, and after allowing 15 minutes for stabilization, total outflow facility was measured for 45 minutes.

Topical epinephrine (seven monkeys) was administered to one eye, with the opposite eye receiving an equal volume of artificial aqueous humor. The fully conscious monkey was treated twice daily for three days, at 7:30 A.M. and 3:30 P.M. On the morning of the fourth day, the animal was anesthetized and treated one last time. Three hours later, each eye was cannulat-

ed with a branched needle, and after a 15-minute stabilization period, total outflow facility was determined for 45 minutes.

Topical timolol (eight monkeys) or betaxolol (12 monkeys) was applied to one eye, with the opposite eye receiving an equal volume of artificial aqueous humor. The animal was treated while conscious and allowed to remain so for the next three hours, at which time it was anesthetized and treated topically and bilaterally with epinephrine. After an additional three hours, each eye was cannulated with a branched needle, and after allowing 15 minutes for stabilization, total outflow facility was measured for 45 minutes. The same protocol, but with intracameral norepinephrine in place of topical epinephrine, was used in ten timolol-pretreated animals and eight betaxolol-pretreated animals.

Results

After the unilateral administration of topical epinephrine as a single dose or twice daily for three days, total outflow facility was significantly higher in the treated eyes than in the contralateral control eyes (Table 1). The facility increases for the single and multiple dose regimens were virtually identical, averaging 33% and 32%, respectively.

After a single unilateral intracameral dose of epinephrine or norepinephrine, facility was also significantly higher in the treated eyes than in the contralateral control eyes. The magnitude of the facility increase produced by the two agonists was essentially the same, averaging 69% for epinephrine and 65% for norepinephrine.

Although the percentage facility increase produced by intracameral epinephrine was approximately twice that produced by single or multiple topical doses, the difference was not statistically significant.

After a single unilateral topical dose of timolol or betaxolol, facility in the treated and control eyes was essentially identical.

After unilateral topical timolol and either bilateral topical epinephrine or bilateral intracameral norepinephrine, facility averaged a statistically significant 40% to 50% higher in the eyes receiving agonist only (Table 2). After the unilateral administration of topical betaxolol and either bilateral topical epinephrine or bilateral intracameral norepinephrine, facility in the two eyes did not differ significantly.

Discussion

Three to four hours after unilateral intracameral administration of epinephrine or norepinephrine, total outflow facility in the treated eye was 65% to 70% higher than in the contralateral control eye. Because both eyes were perfused simultaneously, the facility difference was above and beyond any increase produced by perfusion-induced washout of resistance-contributing material from the trabecular meshwork.[22,23] Earlier studies from our laboratory employed the same monkey species, agonist doses, and drug administration and perfu-

TABLE 1

TOTAL OUTFLOW FACILITY AFTER THE UNILATERAL ADMINISTRATION OF ADRENERGIC DRUGS*

DRUG (DOSE [μG], ROUTE)	NO. OF ANIMALS	TREATED GROUP	CONTROL GROUP	TREATED GROUP/CONTROL GROUP
Epinephrine (600, topical)	8	0.46 ± −0.10	0.36 ± 0.09	1.33 ± 0.11†
Epinephrine (600, topical)‡	7	0.43 ± −0.10	0.33 ± 0.08	1.32 ± 0.09§
Epinephrine (10, intracameral)	8	0.85 ± −0.26	0.50 ± 0.13	1.69 ± 0.24†
Norepinephrine (10, intracameral)	9	0.43 ± −0.05	0.30 ± 0.05	1.65 ± 0.22‖
Timolol (180, topical)	6	0.30 ± −0.06	0.29 ± 0.03	1.03 ± 0.07
Betaxolol (180, topical)	6	0.24 ± −0.03	0.27 ± 0.06	0.99 ± 0.10

*Facility data are mean ± S.E.M. $\mu l \times min^{-1} \times mm\ Hg^{-1}$. Facility measurements encompassed hours 3.25 through 4.0 after dosing.

†Significantly different from 1.0 by the two-tailed paired *t*-test: P = .03.

‡Epinephrine given twice daily, facility measured on day 4.

§Significantly different from 1.0 by the two-tailed paired *t*-test: P = .01.

‖Significantly different from 1.0 by the two-tailed paired *t*-test: P = .02.

TABLE 2
TOTAL OUTFLOW FACILITY AFTER THE BILATERAL ADMINISTRATION OF EPINEPHRINE OR NOREPINEPHRINE FOLLOWING THE UNILATERAL ADMINISTRATION OF TIMOLOL OR BETAXOLOL*

DRUG (DOSE [μG], ROUTE)	NO. OF ANIMALS	AGONIST	ANTAGONIST + AGONIST	AGONIST/AGONIST + ANTAGONIST
Timolol (180, topical) + epinephrine (600, topical)	8	0.37 ± 0.06	0.20 ± 0.05	1.41 ± 0.10†
Timolol (180, topical) + norepinephrine (10, intracameral)	10	0.41 ± 0.09	0.31 ± 0.06	1.48 ± 0.21‡
Betaxolol (180, topical) + epinephrine (600, topical)	12	0.45 ± 0.07	0.41 ± 0.06	1.17 ± 0.12
Betaxolol (180, topical) + norepinephrine (10, intracameral)	8	0.36 ± 0.05	0.32 ± 0.04	1.16 ± 0.13

*Facility data are mean ± S.E.M. $\mu l \times min^{-1} \times mm\ Hg^{-1}$. Facility measurements encompassed hours 6.25 through 7.0 and 3.25 through 4.0 after antagonist and agonist dosing, respectively.

†Significantly different from 1.0 by the two-tailed paired *t*-test: P = .003.

‡Significantly different from 1.0 by the two-tailed paired *t*-test: P = .05.

sion technique, but used a 30-minute, baseline facility determination (immediately before drug administration) as a control to calculate the drug effect. This apparent effect was in turn adjusted downward by 15% for washout, based on separate experiments that quantitated the magnitude of the washout phenomenon under those specific experimental conditions.[4-6,23] After adjustment, the facility-increasing effect of the same intracameral doses of epinephrine and norepinephrine 15 to 35 minutes after drug administration was approximately 25% to 35%[5,6]; larger doses had a lesser effect.[4] Although subject to some of the uncertainties of retrospective "controls," this comparison suggests that the full facility-increasing effect of epinephrine and norepinephrine develops over a longer time than that of pilocarpine, which is mediated by ciliary muscle contraction.[18,24]

Epinephrine's effect on total outflow facility appears to represent increased facility across the trabecular meshwork or inner wall of Schlemm's canal,[6] and to be mediated by a β-adrenergic receptor[8]–cyclic adenosine monophosphate mechanism in the trabecular endothelial cells.[25] Recent evidence suggests that the physical change responsible for the increased hydraulic conductivity may be related to cytoskeletal alterations and subsequent shape changes in the trabecular endothelium[26] (Robinson and Kaufman, unpublished data). If such shape changes promoted increased washout of resistance-contributing extracellular material from the meshwork, facility would increase, but perhaps rather slowly, especially at the low spontaneous aqueous flow rate (1 to 1.5 μl/min in cynomolgus monkeys, 2 to 2.5 μl/min in humans).[27-30] This hypothesis neither requires nor precludes a quantitative or qualitative metabolic effect on the synthesis or degradation of meshwork extracellular material induced by catecholamines and mediated by β-adrenergic receptors and cyclic adenosine monophosphate. It does imply that downward adjustment of the apparent epinephrine effect for washout may not be entirely appropriate. During the 45-minute facility-measuring period, facility was higher but did not increase at a faster rate in the eyes treated with epinephrine or norepinephrine only compared to the contralateral perfusant or agonist + antagonist eyes. Although this does not disprove the increased washout hypothesis (for example, the effect could have peaked earlier than three hours), it does not support it.

Three to four hours after the unilateral topical administration of epinephrine, total outflow facility in the treated eye was approximately 33% higher than in the contralateral control. Although this was not statistically significantly different from the approximately 70% increase seen after the intracameral administration of epinephrine, it suggests a lesser response. We cannot be sure, however, that the topical dose used was maximal, as was the intracameral dose. Although this topical dose is probably near-maximal for the human,[22] it may not have been for the more heavily pigmented monkey eye. There could also be relevant species differences in penetration of or actual responsiveness to the drug. If the topical dose was maximal in our monkeys, the difference in response to topical vs intracameral dosing, if real, could reflect differential effects of drug administered by the different routes on specific parts of the outflow system. For instance, constriction of

Schlemm's canal or the venous channels distal to it, which would more likely occur after a large topical than a small intracameral epinephrine dose, might decrease facility[5,6] and thus partially counteract the facility-increasing effect on the trabecular endothelium.

In our monkeys, three days of twice daily topical epinephrine produced the same percentage facility increase as a single topical dose. In humans, it may require weeks or months of twice daily epinephrine treatment to attain the maximum facility response.[10] Although our data do not exclude the possibility of such a longer-developing effect in the monkey, they do indicate the absence of any such enhancement within the first few days of repeated dosing.

As in the human,[14,16] neither timolol nor betaxolol affected outflow facility in our monkeys. Because trabecular facility constitutes more than 90% of total facility in the monkey,[31] this indicates that there is either no or only subthreshold ambient facility-affecting β-adrenergic tone in the trabecular endothelium of the conscious human or the pentobarbital-anesthetized monkey.

Timolol pretreatment completely prevented the facility-increasing effect of epinephrine and norepinephrine, indicating that both agonists increased facility by means of a β-adrenergic receptor-mediated mechanism. Pretreatment with the same dose of betaxolol did not prevent the facility-increasing effect of either epinephrine or norepinephrine, indicating that the receptor mediating the effect of both agonists was of the β_2 subtype. These findings are consistent with tonographic studies in the human, which indicate that timolol, but not betaxolol, blocks the facility-increasing effect of epinephrine[12,14,16]; and ligand binding and autoradiographic studies in cultured human trabecular cells and trabecular meshwork from human autopsy eyes,[8,32] which indicate the presence of β_2, but not β_1 or α-adrenergic receptors.

ACKNOWLEDGMENTS

Alcon Laboratories, Inc., Fort Worth, Texas, donated commercial ophthalmic epinephrine hydrochloride (Glaucon 2%), commercial ophthalmic betaxolol hydrochloride (Betoptic 0.5%), and crystalline betaxolol hydrochloride. Merck, Sharp and Dohme, Inc., West Point, Pennsylvania, donated commercial ophthalmic timolol maleate (Timoptic 0.5%) and crystalline timolol maleate.

References

1. Bárány, E. H.: Topical epinephrine effects on true outflow resistance and pseudofacility in vervet monkeys studied by a new anterior chamber perfusion technique. Invest. Ophthalmol. 7:88, 1968.

2. Bill, A.: Early effects of epinephrine on aqueous humor dynamics in vervet monkeys (*Cercopithecus ethiops*). Exp. Eye Res. 8:35, 1969.

3. Becker, B., Pettit, T. H., and Gay, A. J.: Topical epinephrine therapy of open angle glaucoma. Arch. Ophthalmol. 66:219, 1961.

4. Kaufman, P. L.: Epinephrine, norepinephrine and isoproterenol dose-outflow facility response relationships in cynomolgus monkey eyes with and without ciliary muscle retrodisplacement. Acta Ophthalmol. 64:356, 1986.

5. Kaufman, P. L., and Rentzhog, L.: Effect of total iridectomy on outflow facility responses to adrenergic drugs in cynomolgus monkeys. Exp. Eye Res. 33:65, 1981.

6. Kaufman, P. L., and Bárány, E. H.: Adrenergic drug effects on aqueous outflow facility following ciliary muscle retrodisplacement in the cynomolgus monkey. Invest. Ophthalmol. Vis. Sci. 20:644, 1981.

7. Pollack, I. P., and Rossi, H.: Norepinephrine in treatment of ocular hypertension and glaucoma. Arch. Ophthalmol. 93:173, 1975.

8. Wax, M. B., Molinoff, P. B., Alvarado, J., and Polansky, J.: Characterization of β-adrenergic receptors in cultured human trabecular cells and in human trabecular meshwork. Invest. Ophthalmol. Vis. Sci. 30:51, 1989.

9. Kaufman, P. L.: Pressure-dependent outflow. In Ritch, R., Shields, M. B., and Krupin, T. (eds.): The Glaucomas, vol. 1. St. Louis, C. V. Mosby, 1989, pp. 219–240.

10. Ballintine, E. J., and Garner, L. L.: Improvement of the coefficient of outflow in glaucomatous eyes. Prolonged local treatment with epinephrine. Arch. Ophthalmol. 66:314, 1961.

11. Zimmerman, T. J., Harbin, R., Pett, M., and Kaufman, H. E.: Timolol and facility of outflow. Invest. Ophthalmol. Vis. Sci. 16:623, 1977.

12. Schenker, H. I., Yablonski, M. E., Podos, S. M., and Linder, L.: Fluorophotometric study of epinephrine and timolol in human subjects. Arch. Ophthalmol. 99:1212, 1981.

13. Miichi, H., and Nagataki, S.: Effects of pilocarpine, salbutamol and timolol on aqueous humor formation in cynomolgus monkey. Invest. Ophthalmol. Vis. Sci. 24:1269, 1983.

14. Allen, R. C., and Epstein, D. L.: Additive effects of betaxolol and epinephrine in primary open angle glaucoma. Arch. Ophthalmol. 104:1178, 1986.

15. Reiss, G. R., and Brubaker, R. F.: The mechanism of betaxolol, a new ocular hypotensive agent. Ophthalmology 90:1369, 1983.

16. Thomas, J. V., and Epstein, D. L.: Timolol and

epinephrine in primary open angle glaucoma transient additive effect. Arch. Ophthalmol. 99:91, 1981.

17. Bárány, E. H.: Simultaneous measurement of changing intraocular pressure and outflow facility in the vervet monkey by constant pressure infusion. Invest. Ophthalmol. 3:135, 1964.

18. Kaufman, P. L., and Bárány, E. H.: Loss of acute pilocarpine effect on outflow facility following surgical disinsertion and retrodisplacement of the ciliary muscle from the scleral spur in the cynomolgus monkey. Invest. Ophthalmol. 15:793, 1976.

19. Kaufman, P. L.: Anticholinesterase-induced cholinergic subsensitivity in primate accommodative mechanism. Am. J. Ophthalmol. 85:622, 1978.

20. Kaufman, P. L., Erickson, K. A., and Neider, M. W.: Echothiophate iodide cataracts in monkeys. Occurrence despite loss of accommodation induced by retrodisplacement of ciliary muscle. Arch. Ophthalmol. 101:125, 1983.

21. Lütjen-Drecoll, E., Kaufman, P. L., and Eichhorn, M.: Long term timolol and epinephrine in monkeys. I. Functional morphology of the ciliary processes. Trans. Ophthalmol. Soc. U.K. 105:180, 1986.

22. Kaufman, P. L.: The effects of drugs on the outflow of aqueous humor. In Drance, S. M., and Neufeld, A. M. (eds.): Glaucoma. Applied Pharmacology in Medical Treatment. Orlando, Grune and Stratton, 1984, pp. 429-458.

23. Erickson, K. A., and Kaufman, P. L.: Comparative effects of three ocular perfusates on outflow facility in the cynomolgus monkey. Curr. Eye Res. 1:211, 1981.

24. Bárány, E. H.: The immediate effect on outflow resistance of intravenous pilocarpine in the vervet monkey, *Cercopithecus ethiops*. Invest. Ophthalmol. 6:373, 1967.

25. Neufeld, A. H., Jampol, L. M., and Sears, M. L.: Cyclic-AMP in the aqueous humor. The effects of adrenergic agents. Exp. Eye Res. 14:242, 1972.

26. Alvarado, J., McHolm, G., Perkins, T., Stilwell, L., Maglio, M., and Murphy, C.: Catecholamine effects on hydraulic conductivity and cell shape in cultured human trabecular meshwork cells. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1989, p. 222.

27. Kaufman, P. L., Bill, A., and Bárány, E. H.: Formation and drainage of aqueous humor following total iris removal and ciliary muscle disinsertion in the cynomolgus monkey. Invest. Ophthalmol. Vis. Sci. 16:226, 1977.

28. Erickson-Lamy, K. A., Kaufman, P. L., McDermott, M. L., and France, N. K.: Comparative anesthetic effects on aqueous humor dynamics in the cynomolgus monkey. Arch. Ophthalmol. 102:1815, 1984.

29. Kaufman, P. L., and Hultsch, E.: Aqueous humor dynamics in the owl monkey with comparison to cynomolgus. Curr. Eye Res. 4:933, 1985.

30. Brubaker, R. F.: Clinical evaluation of the circulation of aqueous humor. In Duane, T. D. (ed.): Clinical Ophthalmology, vol. 3. Philadelphia, Harper and Row, 1987, pp. 1–7.

31. Kaufman, P. L.: Aqueous humor dynamics. In Duane, T. D. (ed.): Clinical Ophthalmology, vol. 3. Philadelphia, Harper and Row, 1987, pp. 1–24.

32. Jampel, H. D., De Souza, E. B., Hotchkiss, M. L., Brown, R. H., and Kuhar, M. J.: Identification and localization of β-adrenergic receptors in human trabecular meshwork. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1985, p. 4.

Accommodative Esotropia After Ocular and Head Injury

Zane F. Pollard, M.D.

Five children lost their ability for motor fusion after traumatic injury to either the eye or head. All patients had the onset of accommodative esotropia within two months of the traumatic episode. The ocular alignment of each child was controlled by the use of spectacles that corrected the accommodative requirements. These patients are unique because they did not show any evidence of accommodative esotropia before their injuries. One child developed accommodative esotropia with a high ratio of accommodative convergence to accommodation. The use of bifocal spectacles controlled the deviation for this child.

THE CONTROL OF BINOCULAR VISION is centrally regulated by the brain. The fusion of some patients breaks down only after years during which a small phoria or a small paresis of an extraocular muscle have been controlled. Some children, whose fusion has been controlled from birth, lose their ability to fuse as accommodative efforts set in. Others lose this ability to fuse only after the onset of ocular or cranial trauma.

Accommodative esotropia has been reported by Parks to occur between 6 months and 7 years of age.[1] The onset of esotropia caused by accommodation has been reported to be present as early as 4 months of age.[2] Manley also reported the onset of accommodative esotropia at an early age with the most common time being around 2½ years of age.[3] Hence, it is well known that accommodative esotropia can occur in early childhood.

I examined five children, ages 5 to 11 years, who had an onset of accommodative esotropia that began shortly after a significant traumatic episode either to the eye or to the head. All five of these patients were successfully treated with spectacles, and a two- to five-year follow-up has shown the accommodative esotropia to be well-controlled. The late onset of the esotropia and its accommodative nature make this manifestation unique. The ophthalmologist should consider accommodation as a cause of esotropia when significant hyperopia is present regardless of the age of onset or the attendant circumstances.

Accepted for publication Nov. 21, 1989.

From the Section of Ophthalmology, Scottish Rite Children's Hospital, Atlanta, Georgia.

Reprint requests to Zane F. Pollard, M.D., 5455 Meridian Mark Rd., Ste. 220, Atlanta, GA 30342.

Case Reports

Case 1

A 6-year-old boy was examined five hours after being attacked by a dog. His mother noticed that his left eye was crossing. Examination disclosed 30 prism diopters of esotropia in the primary position at distance and near with orthophoria in right gaze and 60 prism diopters of esotropia in left gaze. He could not abduct the left eye past the midline. He had a tear in the conjunctiva over the left lateral rectus muscle area with a large subconjunctival hemorrhage from the 12 to 6 o'clock meridian temporally. There were numerous small lacerations of the face. He underwent surgery that evening, during which the left lateral rectus muscle was found to be totally severed from its attachment to the sclera. The muscle was intact but was located about 7 mm posterior to its original insertion. The muscle was sutured back to its original insertion, and the facial cuts closed after débridement. Two weeks postoperatively, the patient had a comitant esotropia of 35 prism diopters in all fields of gaze at distance and near. Cycloplegic refraction was a +6.00 refractive error in each eye. He was able to tolerate a +5.00 lens in each eye in a postcycloplegic state. One month later, he was orthophoric with his spectacles at distance and near with a constant esotropia of 35 prism diopters at distance and near without his spectacles. He fused the Worth 4-Dot test at distance and near. He had

40 seconds of near stereoscopic acuity measured with the Titmus test. A three-year follow-up showed no change. Photographs taken before the dog bite showed no strabismus. There was no history of any ocular abnormality.

Case 2

The left cornea of a 5-year-old boy was accidently penetrated with a pair of scissors. The patient had no history of ocular problems, and his examination showed his eyes to be straight. He underwent surgery to repair a corneal laceration that extended from the 9 o'clock meridian of the corneoscleral limbus for 4 mm onto the cornea in a vertical direction. A prolapsed iris was reposited. The postoperative course was unremarkable, and the patient's corneal sutures were removed one month later. Visual acuity at this time was R.E.: 20/20 and L.E.: 20/200 uncorrected. Twenty diopters of esotropia was present at distance in all fields of gaze with 40 diopters at near. Cycloplegic refraction showed +2.25 refractive error in the right eye with +2.50 +3.00 axis 50 in the left eye. This refraction was given in spectacles with a bifocal of +2.50 for each eye. Full-time patching was started on the right eye. One month later, the child had a visual acuity of R.E.: 20/20 and L.E.: 20/60. The decreased visual acuity in his left eye was secondary to the amblyopia that occurred because of 3 diopters of astigmatism. The laceration was outside of the visual axis. With spectacles, the eyes were orthophoric at distance and had 20 prism diopters of esotropia at near with orthophoria at near through the bifocals. He suppressed the left eye at distance and fused at near through the bifocal on the Worth 4-Dot test. He had 140 seconds of near stereoscopic acuity with the Titmus test. His visual acuity has not improved in the injured eye, but his motility status has remained constant for the past two years. Photographs taken before the injury showed no strabismus.

Case 3

An 8-year-old girl was in a car accident, after which she was unconscious for about 30 minutes. She was hospitalized overnight for observation, and a computed tomographic scan showed the brain to be normal. Ophthalmologic examination the next day showed right sixth nerve palsy. She was unable to abduct the right eye past the midline. There was no evidence of any ocular trauma. Visual acuity was 20/25 in each eye, with 30 prism diopters of esotropia in the primary position at distance and 20 prism diopters of esotropia at near in the primary position. There were 60 prism diopters of esotropia in right gaze with orthophoria in left gaze. The patient had already developed a right facial turn to help rid herself of her diplopia. Two months later, the patient had full abduction of her right eye but was left with a comitant esotropia of 35 prism diopters at distance and near in all fields of gaze. Cycloplegic refraction was +4.50 in each eye, but the patient could tolerate only a +3.00 lens in each eye in a postcycloplegic state. Spectacles were prescribed, and one month later she was orthophoric in all fields of gaze at distance and near. She fused the Worth 4-Dot test at distance and near. She had 40 seconds of near stereoscopic acuity with the Titmus test. A five-year follow-up shows her to be doing well. She has replaced her spectacles with contact lenses. No amblyopia developed. Photographs taken before the motor vehicle accident showed no evidence of any strabismus, and there was no history of any ocular problem before this episode.

Case 4

An 11-year-old boy was examined in the emergency room after sustaining an injury to his left eye with a hockey puck. Visual acuity was R.E.: 20/20 and L.E.: 20/400. There was complete closure of the eyelids of the left side because of a large hematoma on the left upper eyelid. A one-half chamber hyphema was present, but there was no rupture of the globe. Ultrasound showed an intact posterior segment. The patient was hospitalized, sedated, and treated with unilateral patching and 6 mg of oral prednisone/kg of body weight/day. He was discharged after five days. His visual acuity was 20/20 in each eye, with all of the hyphema having cleared. Patching with a metal shield was continued for two weeks. Two months later, he was examined, and for the first time he had a comitant esotropia of 25 prism diopters at distance and near and in all fields of gaze. Cycloplegic refraction was +6.75 in each eye. He accepted a +4.50 lens in each eye in a postcycloplegic state. Spectacles were prescribed, and six weeks later he was orthophoric at distance and near with his spectacles. He could fuse the Worth 4-Dot test at distance and near with his spectacles, and he had 60 seconds of near stereoscopic acuity with the Titmus test. His motility status has remained unchanged over a three-

year follow-up. Photographs taken before the injury showed no strabismus, and there was no history of any ocular problems. He remains esotropic without his spectacles.

Case 5

A 6-year-old boy had his left eye clawed by a cat and was treated by an ophthalmologist for pain and a crossed eye. A large linear corneal abrasion was noted as well as a 45-prism diopter esotropia in the primary position at distance with 60 diopters of esotropia in left gaze and orthophoria in right gaze. The patient was unable to abduct the left eye past the midline. At surgery, the area of the left lateral rectus muscle was explored, and the lateral rectus muscle was seen to have been severed in half 5 mm posterior to its insertion with the distal end found 10 mm from the corneoscleral limbus. The 5-mm stump at the insertion was removed, and the distal end was reinserted at the original insertion. A reanastomosis to the distal end was not possible because the proximal stump was too ragged. Postoperatively, the patient showed 25 prism diopters of esotropia in the primary position at distance and near, and he could abduct the left eye 20 degrees. Over the next two months, abduction became full with a comitant esotropia of 25 prism diopters at distance and near, but amblyopia had set in, with a visual acuity of R.E.: 20/20 and L.E.: 20/100. Cycloplegic refraction at this time showed +5.00 refractive error in each eye. He was able to tolerate a +4.00 lens in a postcycloplegic state, and with this refraction his eyes were orthophoric at distance and near. With patching, the visual acuity in the left eye returned to 20/30. A five-year follow-up has shown no change. With his spectacles, the patient could fuse the Worth 4-Dot test at distance and near. He had 60 seconds of near stereoscopic acuity measured with the Titmus test. Photographs taken before the injury showed no evidence of strabismus. There was no history of any eye problems preceding this incident.

Discussion

All five patients developed an accommodative esotropia after an injury either directly to the eye or the head. All patients responded to conventional spectacles. One required bifocals to control a large accommodative convergence to accommodation ratio associated with accommodative esotropia, which had its onset after a corneal laceration. Von Noorden[4] reported accommodative esotropia developing after brief periods of occlusion, and he stressed that this may occur even during adolescence or adulthood. One of his patients was a 5-year-old who had an esophoria of 8 prism diopters at distance and 10 at near, which changed to 18 prism diopters of esotropia at distance and 45 prism diopters of esotropia at near after trauma that shut the eyelids of one eye for two days. The patient was successfully treated with spectacles.[5] Swan[6] described a series of patients in whom a large-angle esotropia occurred after patching for amblyopia. Holland,[7] in 1962, reported the onset of esotropia in a patient who was patched for a corneal laceration. Most patients who have the onset of esotropia after patching have some fusional ability, which is temporarily disrupted with patching. A latent deviation becomes manifest when the patching is discontinued. In some patients, the deviation is only temporary and fusional ability will be regained after the patch is removed. In others, the deviation will remain, and surgery will be required to straighten the eyes. At least three months and possibly six months should pass before advising surgery because some patients may take this long to regain their fusional status.

Raab,[8] in an extensive treatise on accommodative esotropia, also reported that the most common time of onset was between ages 1 and 2 years. The increase in hypermetropia in his patients with accommodative esotropia from ages 3 to 7 years was small, and the decrease from ages 8 to 13 years was also believed to be insignificant. Of 192 patients followed up, 33 (17%) developed deterioration with the appearance of a partial nonaccommodative component. In the group that had deterioration, two had the accommodative convergence to accommodation ratio become abnormal, and six who had abnormal accommodative convergence to accommodation ratios developed normal' accommodative convergence to accommodation ratios despite the deterioration. The amount of hypermetropia was not believed to be a significant factor in the deterioration. The development in patients with moderate to severe degrees of hypermetropia who have no strabismus is puzzling; such patients should develop accommodative symptoms as they reach their

teens and early 20s. Obviously, trauma of an ocular or cranial nature will decompensate some into accommodative esotropia, such as that which occurred in the children in this study.

If a high accommodative convergence to accommodation ratio or a significant hypermetropia are present, spectacles should be tried before surgery, because there is a possibility that the deviation may be accommodative in nature. This possibility should be considered even if the precipitating event was trauma without any previous history of strabismus. The age of the patient should not discourage one from considering accommodative elements; this series included one patient aged 11 years and another aged 8 years. Additionally, if the patient is still in the amblyogenic age (up to 8 or 9 years of age[9,10]), amblyopia may occur shortly after the onset of the strabismus in some patients and must be treated. These patients characteristically will not have a history of even a phoria because their fusional reserves have been strong enough to align their eyes until the onset of the traumatic incident. In children 5 years of age and younger, the full cycloplegic refraction can be given. After five years of age, often the patient will not accept the full cycloplegic refraction. In such a case, the patient is given the most hyperopic correction acceptable with reasonable visual acuity in a noncycloplegic state, which is usually 20/30.

References

1. Parks, M. M.: Concomitant esodeviations. In Ocular Motility and Strabismus. Hagerstown, Harper and Row, 1975, p. 99.

2. Pollard, Z. F.: Accommodative esotropia during the first year of life. Arch. Ophthalmol. 94:1912, 1976.

3. Manley, D. R.: Accommodative esotropia. In Horizontal Ocular Deviations. St. Louis, C. V. Mosby, 1971, p. 59.

4. Von Noorden, G. K.: Esodeviations. In Burian, H. M., and Von Noorden, G. K. (eds.): Binocular Vision and Ocular Motility, ed. 3. St. Louis, C. V. Mosby, 1985, p. 280.

5. Von Noorden, G. K.: Special forms of strabismus. In Burian, H. M., and Von Noorden, G. K. (eds.): Binocular Vision and Ocular Motility, ed. 3. St. Louis, C. V. Mosby, 1985, p. 389.

6. Swan, K. C.: Esotropia following occlusion. Arch. Ophthalmol. 37:444, 1947.

7. Holland, G.: Über den akuten Strabismus convergens concomitans. Klin. Monatsbl. Augenheilkd. 140:373, 1962.

8. Raab, E. L.: Etiologic factors in accommodative esodeviations. Trans. Am. Ophthalmol. Soc. 80:657, 1982.

9. Parks, M. M.: Amblyopia. Treatment of the sensorial adaptations and amblyopia. In Parks, M. M. (ed.): Ocular Motility and Strabismus. Hagerstown, Harper and Row, 1975, pp. 85–98.

10. Rabinowicz, I. M.: Amblyopia. In Harley, R. D. (ed.): Pediatric Ophthalmology, ed. 2. Philadelphia, W. B. Saunders, 1983, pp. 324–325.

Myopia Induced by Vitreous Hemorrhage

Mariannette J. Miller-Meeks, M.D., Stephen R. Bennett, M.D., Ronald V. Keech, M.D., and Christopher F. Blodi, M.D.

Six of 11 children developed myopia in one eye after vitreous hemorrhage. None had retinopathy of prematurity, glaucoma, aphakia, or scleral buckling. In seven children developing vitreous hemorrhage before 1 year of age, six exhibited a myopic anisometropia in the affected eye of 1.37 to 12.00 diopters (mean, −4.7 diopters; S.D., 4.0). The degree of myopia correlated with the age of onset and duration of media opacification. In the child without myopia, the hemorrhage did not obscure the posterior pole. None of the four children whose hemorrhage occurred after 2½ years of age showed myopic anisometropia (mean, +0.16 diopters; S.D., 0.24). We conclude that vitreous hemorrhage occurring in infancy is strongly associated with the development of myopia in the affected eye.

Although myopia occurs in approximately 33% of young adults in the western world,[1] its cause remains unknown. Although genetic factors have an undisputed role in the course of ocular development, the influence of environmental factors such as nutrition or accommodation are less well established.

Recent investigations have suggested that a visually dependent feedback mechanism is necessary for emmetropization. It has been suggested that the deprivation of patterned visual stimulation has myopic effects on the infant eye. More specifically, it has been demonstrated that eyelid suturing of monkeys, tree shrews, cats, and chickens during infancy creates a shift toward myopia in the deprived eye.[2-8] This myopic shift is attributed to an increase in the axial eye length presumably because of a loss of a feedback mechanism involved in the regulation of ocular growth. This phenomenon is not intrinsically related to eyelid suturing, because myopia has been induced in animals visually deprived at an early age by corneal opacification[9] and by translucent or optical occluders.[10-12] Additionally, myopia does not occur in monkeys whose eyelids are sutured at a young age but who are raised in the dark,[13] negating the role of absolute deprivation. The relationship between deprivation of patterned visual stimulation and myopia has also been demonstrated in humans by examining the refractive error of patients with unilateral congenital cataracts, corneal opacification, blepharoptosis, and hemangiomas of the upper eyelid in infants.[14-19] It is thus hypothesized that the lack of a clear retinal image acts as a mechanism to deregulate ocular growth during maturation, which leads to myopia presumably because of an increase in axial length.

If early visual stimulation is important for ocular development, then any cause of patterned visual deprivation in infancy may result in myopia. After observing an isolated case of severe myopia after neonatal vitreous hemorrhage, we decided to study the possible association of vitreous hemorrhage in childhood and myopia.

Subjects and Methods

A list of patients who had a diagnosis of vitreous hemorrhage or who underwent vitrectomy seen in the pediatric eye clinic of our institution was generated by computer. If an additional diagnosis of aphakia, retinopathy of prematurity, glaucoma, or a history of a scleral buckling procedure was identified, these patients were excluded from study. On chart review, patients were also excluded if no record of refractive error was documented. Eleven eli-

Accepted for publication Nov. 27, 1989.

From the Department of Ophthalmology, University of Iowa, Iowa City, Iowa. This study was presented in part at the annual meeting of the Association for Research in Vision and Ophthalmology, Sarasota, Florida, May 3, 1989. This study was supported in part by an unrestricted grant from Research to Prevent Blindness, Inc., New York, New York.

Reprint requests to Christopher F. Blodi, M.D., Department of Ophthalmology, University of Iowa Hospitals and Clinics, Iowa City, IA 52242.

gible patients were identified. Those with a documented vitreous or preretinal hemorrhage occurring before the age of 1 year underwent a complete ophthalmologic examination, including visual acuity, cycloplegic refraction, indirect ophthalmoscopy, and measurement of corneal diameter. Recording of axial eye lengths by standardized A-scan ultrasonography was attempted; however, because of the young age of our subjects, reliable measurements could only be obtained in three children, and results were suboptimal in another child.

Results

Of the 11 patients included in this study, six (55%) were boys and five (45%) were girls. Six of these patients developed vitreous or preretinal hemorrhages obscuring the posterior pole between birth and 3 months of age (Table 1). An additional child who acquired a vitreous hemorrhage at birth but in whom the hemorrhage location was noted only in the far periphery is excluded from this table. The predominant cause of hemorrhage in the younger age group was birth trauma by forceps delivery or suspected birth trauma. Other sources for hemorrhage in the younger age group include Terson's syndrome and child abuse. Two subjects were premature; however, repeated examinations showed normal retinas with the exception of vitreous or preretinal hemorrhages. Patient 5 (Table 1) and the child whose hemorrhage was only in the periphery are the subjects who were premature.

The primary causative agent in the children whose onset of hemorrhage occurred after 2½ years of age was blunt or penetrating trauma (Table 2). Patient 10 was noted to have vitreous hemorrhage after sustaining possible blunt trauma following strabismus surgery.

Of those children who acquired a vitreous or preretinal hemorrhage obscuring the posterior pole before the age of 1 year, there was a strong shift toward anisometropic myopia in the affected eye. The median difference, calculated by spherical equivalent, between the affected and unaffected eye was −4.7 diopters (range, −1.37 diopters to −10.75 diopters) (Fig. 1). The patient who had a far peripheral vitreous hemorrhage that did not obscure the posterior pole had +0.75 diopters of anisometropia in the right eye and +1.00 diopters in the affected left eye. Those children with an acquired vitreous hemorrhage after the age of 2½ years did not demonstrate any myopic tendency (Table 2). In this group, the median difference was +0.16 diopters (range, plano to +0.50 diopters).

The degree of myopia in the affected eye also increased with the duration of media opacification (Fig. 2). Those infants with the greatest degree of anisometropic myopia also had long-

TABLE 1
ONSET OF HEMORRHAGE BEFORE 1 YEAR OF AGE

PATIENT NO.	AGE OF ONSET	CAUSE	DURATION (MOS)	CURRENT REFRACTION	SPHERICAL EQUIVALENT	CURRENT VISUAL ACUITY	AGE AT LAST FOLLOW-UP (YRS)
1	Birth	Forceps delivery (L.E.)	7	R.E.: +4.00	+4.00	20/30	3.3
				L.E.: −8.00	−8.00	20/100−	
2	Birth	Forceps delivery (R.E.)	<3	R.E.: +0.50	+0.50	20/30+	3.5
				L.E.: −2.25 +0.50	−2.00	20/30−	
3	1 mo	Terson's syndrome (R.E.)	6	R.E.: −2.50 −2.50	−1.25	Central, steady, and unmaintained	3.3
				L.E.: +2.25 +0.50	+2.50	Central, steady, and unmaintained	
4	3 mos	Unknown (L.E.)	2	R.E.: −0.50 +0.50	−0.25	20/30	4.0
				L.E.: −3.00 +1.50	−2.25	20/800	
5	Birth	Birth trauma (R.E.>L.E.)	R.E., 4; L.E., 1	R.E.: −3.25 +2.25	−2.12	Central, steady, and unmaintained	2.5
				L.E.: −1.00 +0.50	−0.75	Central, steady, and unmaintained	
6	2 mos	Child abuse (L.E.)	7	R.E.: +3.50	+3.50	Central, steady, and unmaintained	2.5
				L.E.: −4.00 +1.75	−3.13	Central, steady, and unmaintained	

TABLE 2
VITREOUS HEMORRHAGE ACQUIRED AFTER ONE YEAR OF AGE

PATIENT NO.	AGE OF ONSET (YRS)	CAUSE	DURATION (MOS)	CURRENT REFRACTION	SPHERICAL EQUIVALENT	CURRENT VISUAL ACUITY	AGE AT LAST FOLLOW-UP (YRS)
7	2½	Combined hamartoma (L.E.)	2	R.E.: −0.25 +0.50	Plano	20/20	6
				L.E.: +0.50	+0.50	20/25	
8	3	Perforating injury (R.E.)	1	R.E.: +0.50 +1.00	+1.00	20/30	10
				L.E.: +1.00	+1.00	20/15	
9	2½	Blunt trauma (R.E.)	3	R.E.: +1.00 +0.75	+1.37	Hand motions	3½
				L.E.: +1.50	+1.50	20/30	
10	10	Blunt trauma (L.E.)	2	R.E.: +0.25 +2.00	+1.25	20/40	12
				L.E.: +0.50 +1.50	+1.25	Counting fingers	

standing vitreous hemorrhage for many months. Those infants with a vitreous hemorrhage of greater than six months' duration had a mean anisometropia of −7.46 diopters compared with only −1.96 diopters in those with a hemorrhage for less than six months.

Each child was examined for signs of glaucoma. None of the children demonstrated any significant difference in corneal diameter between the affected and unaffected eye or optic disk abnormalities commonly seen with glaucomatous nerve damage. In three patients, intraocular pressures were obtained and were equal in both eyes.

Four children had axial eye length measurements. Patient 3 (Table 1) displayed no difference in axial eye length measurements; however, both globes at 20.4 mm were smaller than normal for this age (average, 22.4 mm). Patient 5 (Table 1) had axial eye lengths of 22.5 mm in the right eye and 22.3 mm in the left eye. This child had bilateral vitreous hemorrhages, and the right eye, which had a longer-lasting hemorrhage, was the more myopic, and had a slightly longer axial eye length. The child who was hyperopic in both eyes and who had only a far peripheral hemorrhage had an axial length of 20.3 mm in the right eye and 20.7 mm in the left eye, which had a hemorrhage. In one other child, we were able to obtain only suboptimal

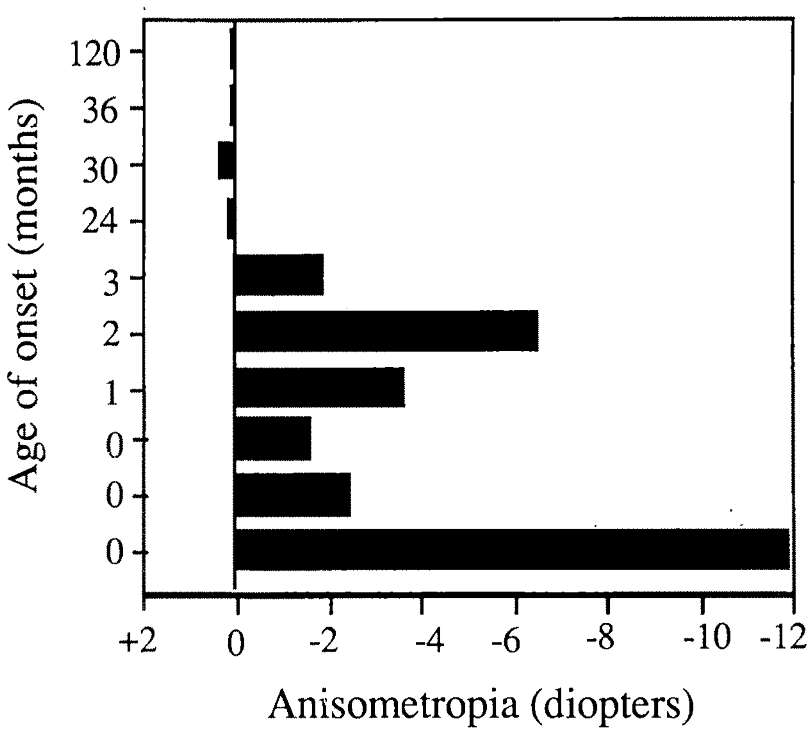


Fig. 1 (Miller-Meeks and associates). Degree of anisometropia vs the age of onset of the vitreous hemorrhage.

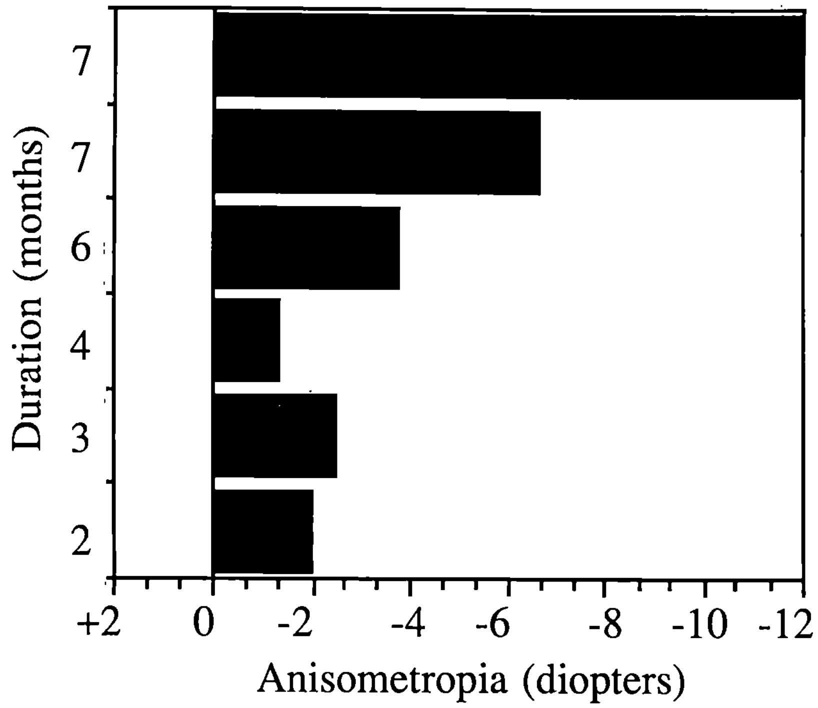


Fig. 2 (Miller-Meeks and associates). Degree of anisometropia vs the duration of vitreous hemorrhage.

axial eye length measurements. Patient 2 (Table 1) had axial eye lengths of 20.7 mm in the right eye and 20.3 mm in the affected left eye, measurements which are slightly shorter than what is recognized as normal for the patient's age. Because these measurements were performed without sedation and by contact probe rather than by immersion, we are unable to comment on the lens dimensions.

Three patients underwent vitrectomy for treatment of their vitreous hemorrhages. Although it is possible that the vitrectomy procedure itself contributed to the myopia, it seems unlikely. Patient 1 (Table 1) and Patients 7 and 8 (Table 2) required vitrectomy. Patient 1 developed −12.00 diopters of anisometropia and Patient 7 demonstrated +0.50 diopters of anisometropia, whereas Patient 8 had no anisometropia.

Discussion

This study documents the effect of infantile vitreous hemorrhage on the refractive status of the eye. We found a strong association of vitreous hemorrhage that obscured the posterior pole and myopia in the affected eye of infants who were visually deprived before the age of 1 year. The magnitude of the associated myopia was also greater depending on the duration of the media opacification. One child whose onset of hemorrhage was at birth but who was hyperopic in both eyes was noted to have a hemorrhage only in the far periphery of the retina.

The concept of monocular form deprivation leading to myopia in the affected eye is not new. Our data are consistent with the report by Rabin and Van Sluyters[14] who found less hyperopia in eyes after surgery for unilateral congenital cataract and marked myopia in eyes with other forms of monocular visual deprivation.

Additionally, there appears to be a critical age at which myopia will no longer occur. In our study, those children whose vitreous hemorrhage occurred after 2½ years of age did not exhibit a shift in their refractive state. Axial eye length measurements on newborn term infants show a rapid elongation of the eye to 22.01 mm by 10 months of age,[20] and this rapid growth phase correlates well with our observations. It seems plausible that the effects of deprivation would be most detrimental at a stage of rapid growth, thus the youngest patients would be most affected. Our axial eye length measurements did not demonstrate a consistent elongation in the more myopic eye. We cannot discern, therefore, if the myopic shift is purely axial in nature or if there is a lenticular component.

It is also recognized that prematurity and low birth weight are associated with an increased

incidence of myopia.[21,22] Patient 5 was premature at 32 weeks' gestation and 1,500 g, had bilateral vitreous hemorrhages, and was myopic in both eyes. The eye with the greater duration of media opacification is also the more myopic eye. The child who had a far peripheral retinal hemorrhage and a hyperopic refraction was premature at 34 weeks' gestation and 1,100 g. This does not exclude prematurity as a causative factor, but it does diminish its impact.

This study supports the theory that emmetropization is a vision-dependent phenomenon and that early monocular deprivation induces a myopic shift in the affected eye. The possibility that vitreous hemorrhage may act as a mechanism for depriving formed visual stimulation in infants is strongly supported. Once identified, these children need frequent follow-up examinations that include cycloplegic refraction even long after the hemorrhage has resolved. Appropriate spectacle correction and patching therapy should be instituted as the situation mandates. The role of vitrectomy surgery is unclear in the management of infantile vitreous hemorrhage. Vitrectomy, however, should be considered in infants with longstanding vitreous hemorrhage. Sonographic axial eye length measurements may also be warranted to determine the characteristics of the induced myopia.

References

1. Angle, J., and Wissmann, D.: The epidemiology of myopia. Am. J. Epidemiol. 111:220, 1980.
2. Wiesel, T., and Hubel, D.: Comparison of the effects of unilateral and bilateral eye closure on cortical unit responses in kittens. J. Neurophysiol. 28:1029, 1965.
3. Wiesel, T., and Raviola, E.: Myopia and eye enlargement after neonatal lid fusion in monkeys. Nature 266:66, 1977.
4. Von Noorden, G. K., and Crawford, M. L. J.: Lid closure and refractive error in macaque monkeys. Nature 272:53, 1978.
5. Sherman, S. M., Norton, T. T., and Casagrande, V. A.: Myopia in lid-sutured tree shrew (*Tupaia glis*). Brain Res. 124:154, 1977.
6. Lauber, J. K., and Oishi, T.: Lid suture in chicks. Invest. Ophthalmol. Vis. Sci. 23:135, 1982.
7. Hubel, D. H., and Wiesel, T. N.: The period of susceptibility to physiological effects of unilateral eye closure in kittens. J. Physiol. 206:419, 1970.
8. Smith, E., and Harwerth, R.: Observations on the effects of form deprivation on the refractive status of the monkey. Invest. Ophthalmol. Vis. Sci. 28:1236, 1987.
9. Wiesel, T., and Raviola, E.: Increase in axial length of the macaque monkey eye after corneal opacification. Invest. Ophthalmol. Vis. Sci. 18:1232, 1979.
10. Wallman, J., and Turkel J.: Extreme myopia produced by modest change in early visual experience. Science 201:1249, 1978.
11. Wallman, J., and Gottlieb, M.: Local retinal regions control local eye growth and myopia. Science 237:73, 1987.
12. Maguire, G., and Smith, E.: Optically induced anisometropia in kittens. Invest. Ophthalmol. Vis. Sci. 23:253, 1982.
13. Raviola, E., and Wiesel, T.: Effect of dark-rearing on experimental myopia in monkeys. Invest. Ophthalmol. Vis. Sci. 17:485, 1978.
14. Rabin, J., and Van Sluyters, R.: Emmetropization. A vision-dependent phenomenon. Invest. Ophthalmol. Vis. Sci. 20:561, 1981.
15. Johnson, C., Post, R., Chalupa, L., and Lee, T.: Monocular deprivation in humans. A study of identical twins. Invest. Ophthalmol. Vis. Sci. 23:135, 1982.
16. Rasooly, R., and BenEzra, D.: Congenital and traumatic cataract. The effect on ocular axial length. Arch. Ophthalmol. 106:1066, 1988.
17. Gee, S., and Tabbara, K.: Increase in ocular axial length in patients with corneal opacification. Ophthalmology 95:1276, 1988.
18. Von Noorden, G. K., and Lewis, R.: Ocular axial length in unilateral congenital cataracts and blepharoptosis. Invest. Ophthalmol. Vis. Sci. 28:750, 1987.
19. Hoyt, C. S., Stone, R. D., Fromer, C., and Billson, F. A.: Monocular axial myopia associated with neonatal eyelid closure in human infants. Am. J. Ophthalmol. 91:197, 1981.
20. Grignola, A., and Rivara, A.: Observations biométriques sur l'oeil des enfants nés terme et des prematurés au cours de la première année. Ann. Oculist. 201:817, 1968.
21. Graham, M. V., and Gray, O. P.: Refraction of premature babies' eyes. Br. Med. J. 1:1452, 1963.
22. Curtin, B. S.: The pathogenesis of congenital myopia. Arch. Ophthalmol. 69:60, 1963.

Late Developing Lesions in Birdshot Retinochoroidopathy

Gisèle Soubrane, M.D., René Bokobza, M.D., and Gabriel Coscas, M.D.

Birdshot retinochoroidopathy is characterized by depigmented spots radiating from the optic disk in association with mild vitritis, retinal vasculitis, and involvement of the optic nerve head. In two patients, we traced the long-term course of uveitis with vitritis, retinal vasculitis, and papillitis that resulted in the typical cream-colored spots of birdshot retinochoroidopathy after seven and eight years, respectively, of follow-up. These observations suggest that in long-standing inflammation of the retinal vasculature and uveal tract, the HLA-A29 antigen should be assessed, because the development of typical lesions of birdshot retinochoroidopathy may be delayed in some patients.

THE CLINICAL FEATURES of birdshot retinochoroidopathy, a chronic intraocular inflammatory process, were delineated and defined as a distinct ocular entity by Ryan and Maumenee.[1] The first description of the disease was probably the case reported by Franceschetti and Babel[2] in 1949. Since then, other designations have been used to describe the disease.[3,4]

The onset of the disease is typically marked by vitritis (with minimal anterior chamber inflammatory reaction), evidence of retinal vasculopathy, edema of the optic disk, and unusual patches of chorioretinitis. These patches appear as multiple, small, cream-colored lesions that are scattered mostly around the optic disk and radiate toward the equator. On fluorescein angiography, the spots show only a mild staining in the venous phase and no leakage.

As more data on birdshot retinochoroidopathy have been gathered, our understanding of the clinical picture of this disorder has evolved as well.[5-8] Some reports have noted complications such as subretinal new vessels,[8,9] optic atrophy,[10] and rhegmatogenous detachments.[6,11] Other reports have emphasized special characteristics of the disease such as electrophysiologic abnormalities[5,12] and an association with the HLA-A29 gene.[13,14] The most prominent feature of the disease is the patterned distribution of the depigmented spots.

We examined two patients who exhibited characteristic birdshot lesions long after the onset of vitritis and vasculitis in choroids that clinically and angiographically were previously normal.

Case Reports

Case 1

A 50-year-old man was referred to one of us (G.C.) in 1975 because of gradual deterioration of vision in both eyes after a chronic intraocular inflammatory disease of unknown origin. Ophthalmic examination showed a number of cells in association with increased haziness of the vitreous body. Ophthalmoscopy disclosed swelling of the optic disks with blurred margins and dilated capillaries. The veins in both eyes showed some irregularity in caliber (Fig. 1, top left and right).

In the early phases of fluorescein angiography, the capillaries of the optic disk leaked heavily. Additionally, leakage was noted in the surrounding peripapillary retinal tissue (Fig. 1, bottom left and right). Retinal vascular leakage and localized staining of the vessel wall of the large retinal veins were observed. The choroid appeared normal in all phases of the angiogram. A thorough systemic workup was noncontributory. Corticosteroid therapy resulted in a slow recovery of visual acuity.

Episodes of vitritis recurred in the subsequent years. In 1983, after seven years of observation, the patient's visual acuity decreased suddenly to R.E.: 20/100 and L.E.: 20/200. At that time, abundant cellular debris was noted in

Accepted for publication Nov. 28, 1989.
From the Eye University Clinic of Creteil, University of Paris-XII, Creteil, France.
Reprint requests to G. Soubrane, M.D., Eye University Clinic of Creteil, Avenue de Verdun 40, Creteil 94010, France.

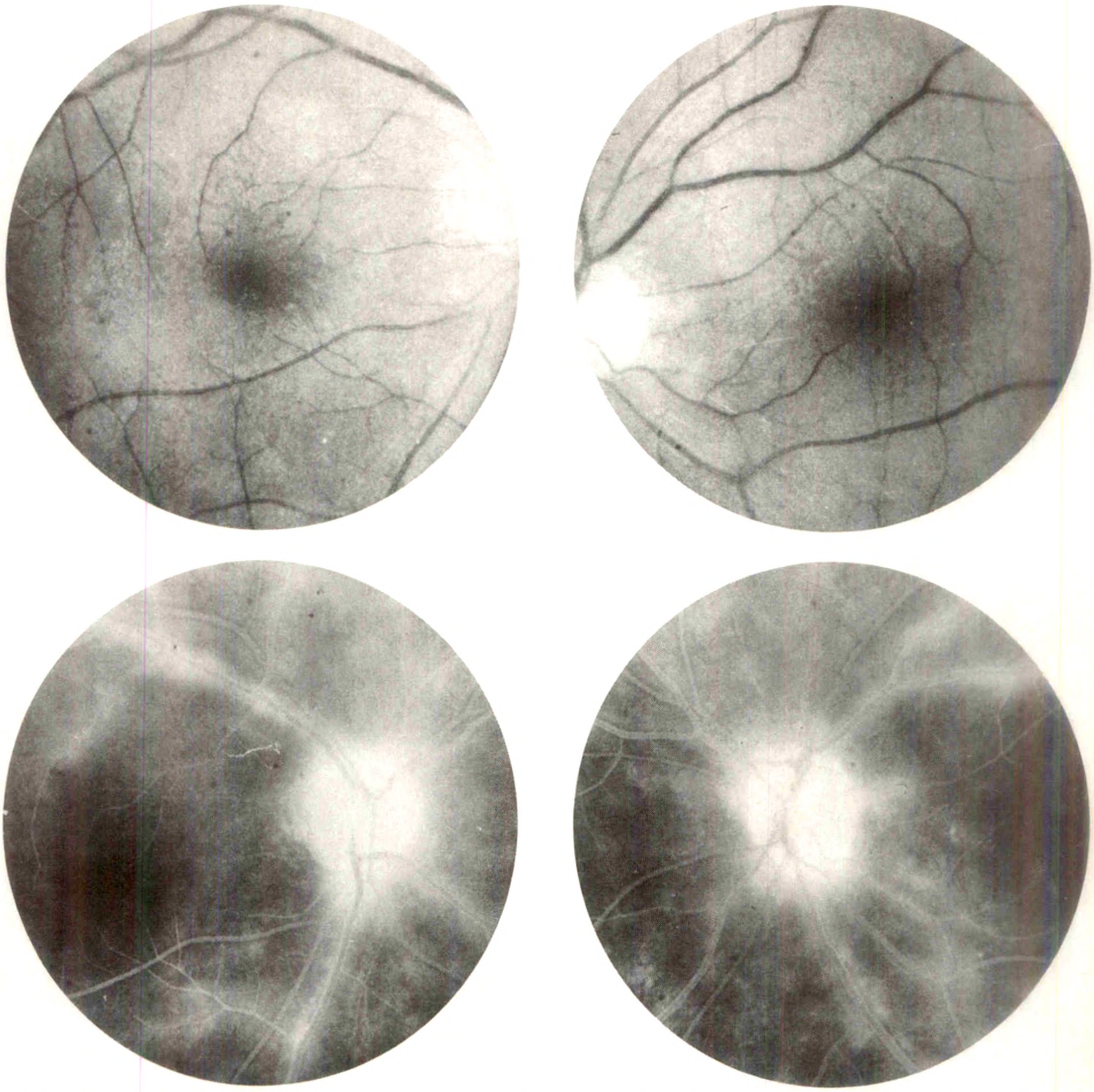


Fig. 1 (Soubrane, Bokobza, and Coscas). Case 1, 1975. Top left, Red-free photograph shows glistening of the temporal macular area and discrete retinal hemorrhages in the right eye. Top right, Veins are discretely dilated. Bottom left and right, The optic nerve in both eyes stains with fluorescein in late phases of fluorescein angiography. The walls of the large veins stain with the dye. Note that the choroidal background fluorescence appears normal in both eyes, including in the peripapillary area.

both anterior and posterior vitreous cavities. Both maculas showed mild edema and surface wrinkling of the internal limiting membrane (Fig. 2, top right). Focal areas of sheathing were observed along some of the veins. The optic nerve heads were pale. On slit-lamp examination, sharply defined, small, round areas of cream-colored lesions were found radiating from the optic nerve head (Fig. 2, top left and right) in both eyes. Deep in the retina were multiple small, plaque-like, hypopigmented zones, which were distributed throughout the posterior pole toward the periphery. The lesions adjacent to the optic disk appeared petaloid.

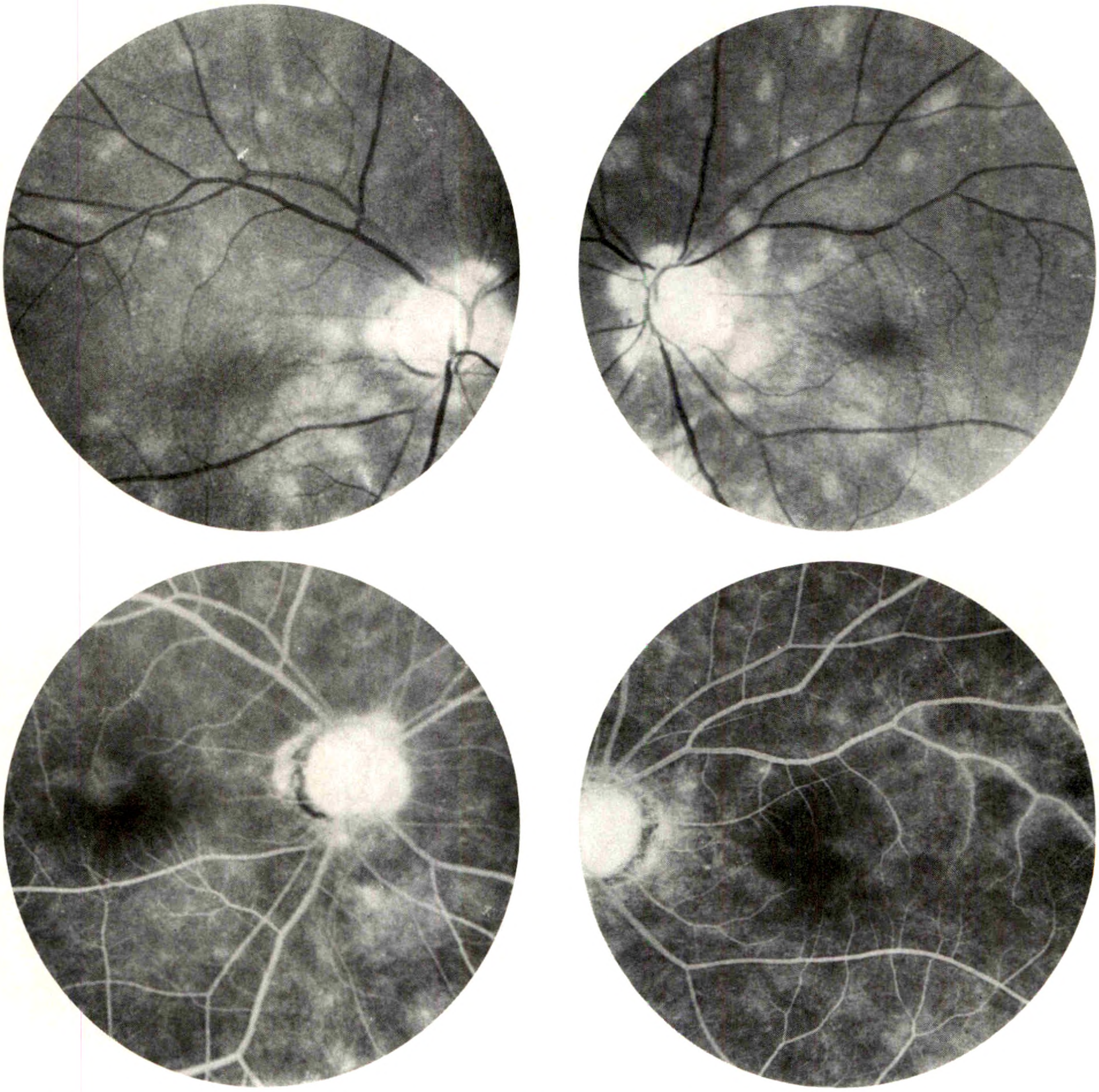


Fig. 2 (Soubrane, Bokobza, and Coscas). Case 1, 1983. Top left, Red-free photograph of the right eye shows subretinal depigmented lesions radiating from the optic disk toward the periphery. Top right, Red-free photograph of the left eye discloses round, punched-out lesions at the nasal border of the disk. Note wrinkling of the internal limiting membrane. Bottom left and right, Late frames of fluorescein angiography show the staining of deep retinal lesions in both eyes. Note some leakage in the temporal macular area in the right eye.

On fluorescein angiography, the atrophic peripapillary patches, which were not present in 1975, showed early hyperfluorescence with late staining (Fig. 2, bottom left). The characteristic hypopigmented subretinal lesions were not visible in the early frames of the angiogram, but became hyperfluorescent later, without leakage (Fig. 2, bottom left and right). After corticosteroid therapy, the macular edema resolved and the visual acuity improved to R.E.: 20/70 and L.E.: 20/80. The patient tested positive for HLA-A29 and HLA-B12 antigens.

On follow-up examination in 1988, the appearance of the fundus was typical of birdshot retinochoroidopathy (Fig. 3, left and right). The optic nerve was surrounded by round,

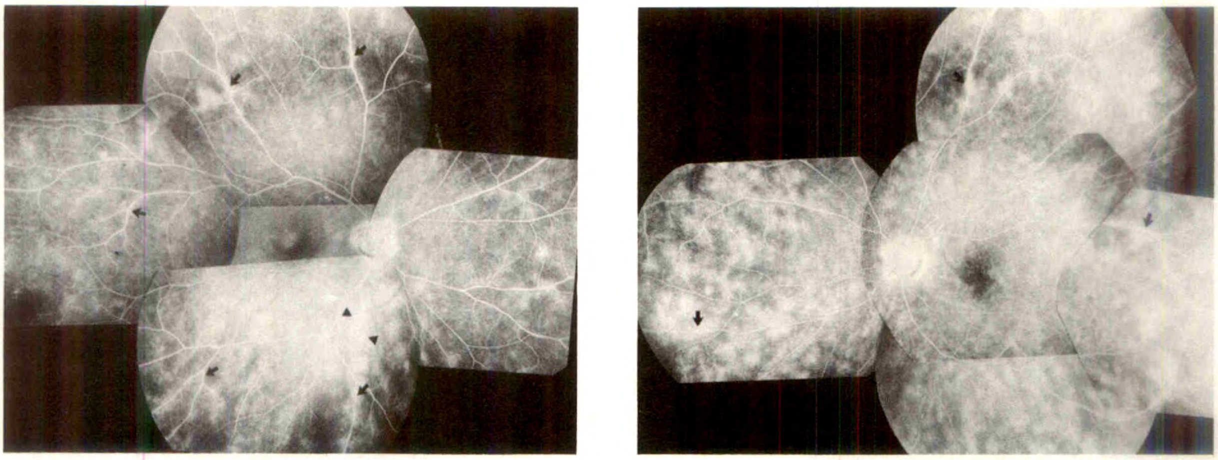


Fig. 3 (Soubrane, Bokobza, and Coscas). Case 1, 1988. Left and right, Fluorescein composites show late staining from the optic nerve and no active leakage of dye from the retinal veins in either eye. Retinal vessels are attenuated and segments are sheathed (arrows). The number of retinochoroidal patches has increased and some have atrophied (arrowhead). No macular edema is visible.

punched-out lesions. The retinal vessels were attenuated and sheathed. The deep chorioretinal patches had increased in number, but some had become atrophic. Discrete staining in the macular area caused by macular wrinkling was observed.

Case 2

A 38-year-old woman was referred to our institution in 1988 because of a 12-year history of bilateral vasculitis and papillitis. In 1976, the referring ophthalmologist noted that the visual acuity in both eyes was 20/25, with cells in the vitreous. A fundus examination disclosed a swollen disk and dilated retinal veins (Fig. 4, top left). On fluorescein angiography, the dilated epipapillary capillaries (Fig. 4, top right) leaked dye (Fig. 4, bottom left). Localized leakage and staining of the large retinal veins were observed on late frames (Fig. 4, bottom left). There was no evidence of cystoid macular edema (Fig. 4, bottom right). Results of a systemic medical examination were unremarkable. The patient received corticosteroid therapy.

Episodes of vitritis recurred in 1977 and in 1979. In the meantime, the clinical and angiographic features of the papillitis and vasculitis decreased. No cystoid macular edema was visible.

In 1981, eight years after onset, visual acuity was R.E.: 20/30 and L.E.: 20/25. Biomicroscopic examination showed that some flare persisted in the vitreous. Multiple round, cream-colored lesions without hyperpigmentation were found nasal to the disk and along the major temporal arcades (Fig. 5, top left and right). A discrete vasculitis was still present (Fig. 5, bottom left), and macular capillaries were normal and without macular edema (Fig. 5, bottom right). Results of HLA testing were positive for HLA-A29.

During the following years, the deep spots progressively extended to the equator. In 1988, cystoid macular edema became obvious and was associated with a slight decrease in visual acuity. A mild staining of the major veins persisted. The lesions around the optic disk resembled petals.

Discussion

Typically, the multiple cream-colored and depigmented deep chorioretinal spots of birdshot retinochoroidopathy occur with the onset of the disease in the nasal retina and radiate toward the periphery in association with vitritis, retinal vasculopathy, involvement of the optic nerve head, and frequent cystoid macular edema. The angiographic features of the patches, which are characterized by normal background fluorescence in the early phase but with late, mild staining, have been discussed extensively.[1,3,8] At present, it is clear that the appearance, extent, and distribution of the lesions change over time.[7]

The latest clinical and angiographic examinations of our patients showed all the characteristic changes of birdshot retinochoroidopathy,

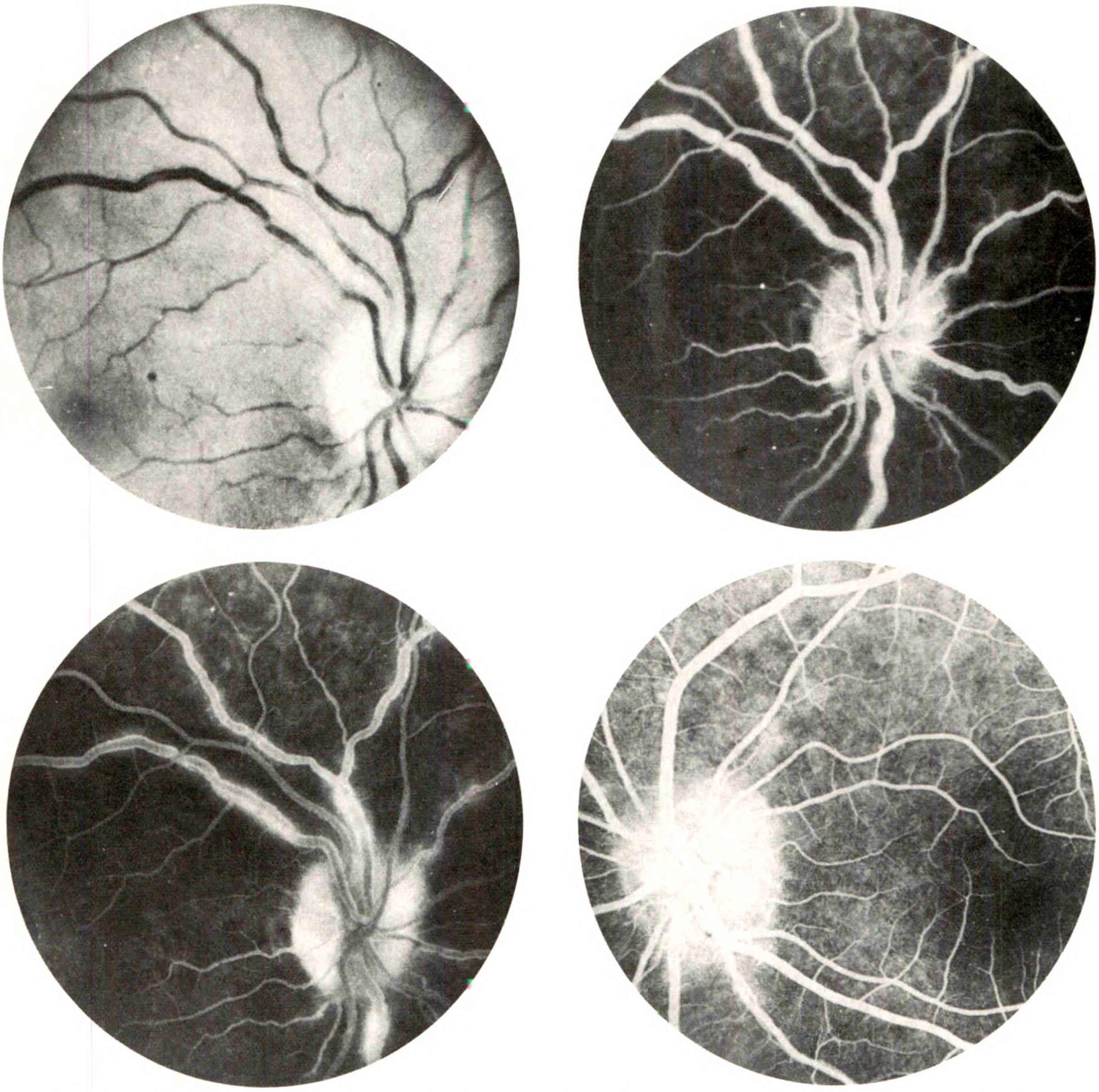


Fig. 4 (Soubrane, Bokobza, and Coscas). Case 2, 1976. Top left, The right optic disk is swollen, and the retinal veins are markedly dilated. No abnormalities are visible at the level of the pigment epithelium in this red-free photograph. Top right, Fluorescein angiogram shows major irregularities on the retinal veins and dilated capillaries at the optic disk. Bottom left, Late frames of fluorescein angiogram show leakage of dye from the optic disk and a segmental staining from the large retinal veins. Bottom right, Capillaries at the optic disk are discretely dilated in the left eye. No cystoid macular edema is noticeable.

even though their bilateral involvement began many years previously as recurrent and chronic retinal vasculitis with nonspecific and mild posterior uveitis. The swollen optic disks exhibited dilated and leaking retinal capillaries.

Retinal vasculitis associated with vitreous cells and papillitis was the initial sign of the disease in our patients. Fundi characteristic of birdshot retinochoroidopathy were visible only after seven and eight years of exacerbation and remission of the vasculitis and vitritis in the two patients. Because the choroid appeared

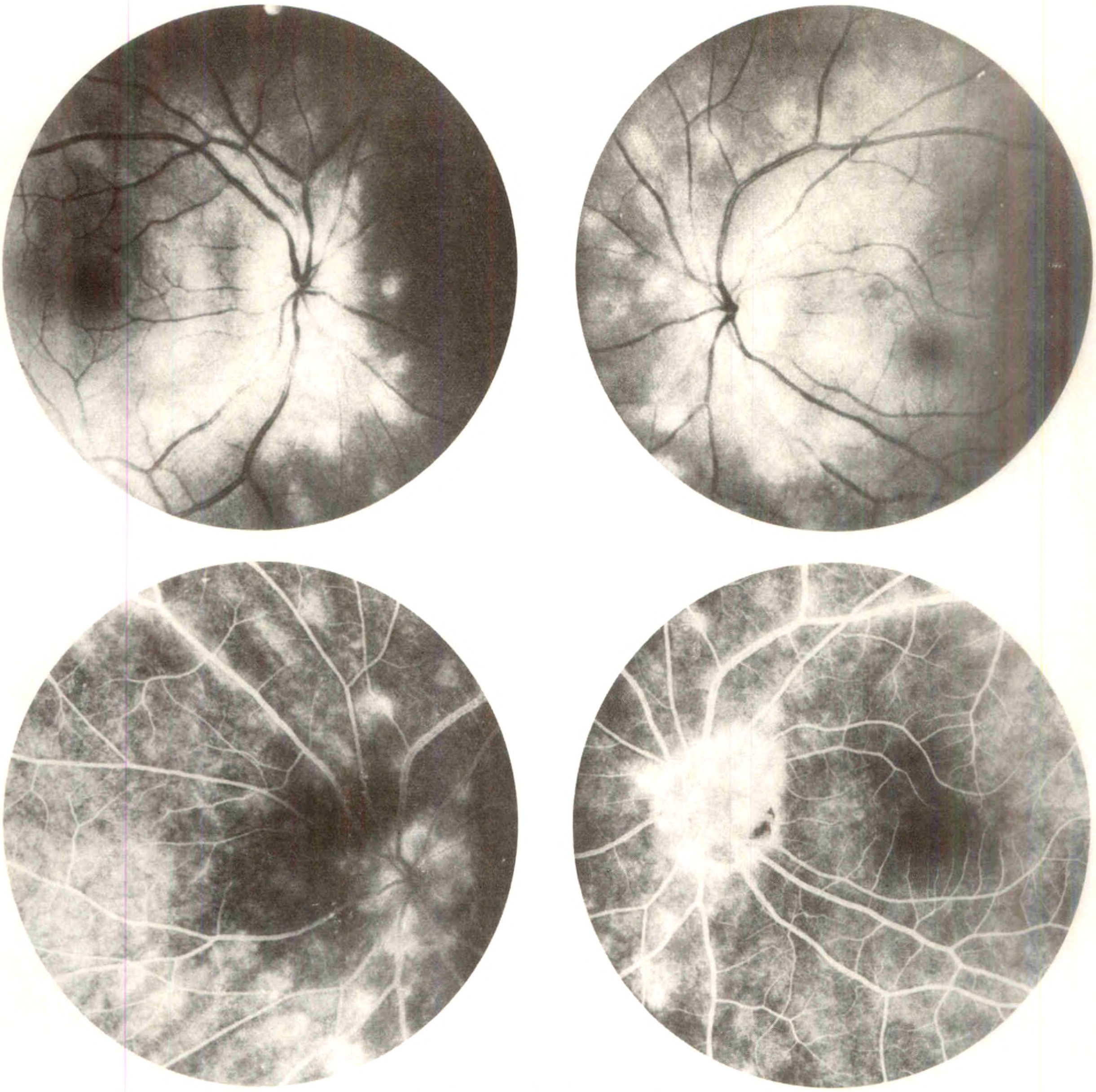


Fig. 5 (Soubrane, Bokobza, and Coscas). Case 2, 1981. Top left and right, Red-free pictures show deep, whitish-colored round patches nasal to the optic disk (right eye) and along the inferior veins (left eye). Bottom left, Deep retinal patches are obvious nasal to the optic disk; they stain with fluorescein on late frames. Bottom right, Peripapillary atrophy has developed. The macular area appears normal.

normal at the onset, the diagnosis of birdshot retinochoroidopathy was a challenge to establish.

It appears from our cases that the mode of onset and clinical characteristics in the early stages of birdshot retinochoroidopathy may vary; the chorioretinal lesions may be delayed for a period of months or even years. These delays before the onset of retinochoroidal patches may result from variations in the site and in the rapidity and extent of involvement of the inflammatory process. These elements, in turn, may be determined by the individual's response to the disorder causing the disease.

Several hypotheses have been made about the pathogenesis of these lesions[1,3,8] and their na-

ture and level of involvement in the eyes. The findings in our patients indicate that the disorder might be secondary to a long-standing retinal vasculitis. Evidence of the choroidal disease would then become apparent with the progressive occurrence of the pale lesions.

Although the functional abnormalities are not pathognomonic of the disease, all of those described in the literature[5,13] imply that the visual loss in patients with birdshot retinochoroidopathy is related to an abnormality of the inner retina that is caused by a vascular disease rather than outer retinal damage as a consequence of choroidal inflammation.

Immunologic data have suggested a strong association between the HLA-A29 antigen and birdshot retinochoroidopathy (95.8% of patients).[12-14] The risk that a person positive for HLA-A29 might acquire birdshot retinochoroidopathy is approximately 200 times greater than it would be for a person not carrying this antigen. Only a small proportion of the HLA-A29–positive population, however, acquires birdshot retinochoroidopathy, which suggests that other as yet unknown factors are involved in the pathogenesis of this disease. Clinical evidence has suggested that birdshot retinochoroidopathy is an inflammatory condition that may involve delayed secondary autoimmune reactions directed against ocular tissue antigens.

Birdshot retinochoroidopathy is considered to be a nosologic entity based on characteristic ophthalmologic findings and clinical course, combined with an exceptionally high association with HLA-A29.

According to the cases described in this study, birdshot retinochoroidopathy may include perhaps late stages of long-standing inflammatory process of the uveal tract or of the retinal vasculature or both, but above all, a specific response to a pathogenic agent in patients carrying the HLA-A29 antigen. This last possibility should be considered in all cases of chronic posterior uveitis of unknown cause.

ACKNOWLEDGMENT

R. Verdet, M.D., Avignon, France, supplied Figure 4.

References

1. Ryan, S. J., and Maumenee, A. E.: Birdshot retinochoroidopathy. Am. J. Ophthalmol. 89:31, 1980.

2. Franceschetti, A., and Babel, J.: La chiriorétinite in taches de bougie, manifestations de la maladie de Besnier-Boeck. Ophthalmologica 118:701, 1949.

3. Gass, J. D. M.: Vitiliginous chorioretinitis. Arch. Ophthalmol. 199:1778, 1981.

4. Amalric, P., and Cuq, G.: Une forme très particulière de choriorétinopathie de grains de riz. Bull. Soc. Ophtalmol. Fr. 81:131, 1981.

5. Kaplan, H. J., and Aaberg, T. M.: Birdshot retinochoroidopathy. Am. J. Ophthalmol. 90:773, 1980.

6. Fuerst, D. J., Tessler, H. H., Fishman, G. A., Yokoyama, M. M., Wyhinny, G. J., and Vygantas, C. M.: Birdshot retinochoroidopathy. Arch. Ophthalmol. 102:214, 1984.

7. Priem, H. A., and Oosterhuis, J. A.: Clinical manifestations in birdshot chorioretinopathy. Br. J. Ophthalmol. 72:646, 1988.

8. Soubrane, G., Coscas, G., Binaghi, M., Amalric, P., and Bernard, J. A.: Birdshot retinochoroidopathy and subretinal new vessels. Br. J. Ophthalmol. 67:461, 1983.

9. Brucker, A. J., Deglin, E. A., Bene, C., and Hoffman, M. E.: Subretinal choroidal neovascularization in birdshot retinochoroidopathy. Am. J. Ophthalmol. 99:40, 1985.

10. De Laey, J. J., and Priem, H. A.: Birdshot chorioretinopathy. An etiological problem. Bull. Soc. Belge Ophtalmol. 193:131, 1981.

11. Laroche, A., Saraux, H., Quentel, G., and Le Hoang, P.: Birdshot chorioretinopathie après décollements de rétine. Origine autoimmune probable. Bull. Soc. Ophtalmol. Fr. 83:1245, 1983.

12. Nussenblatt, R. B., Mittal, K. K., Ryan, S. J., Green, W. R., and Maumenee, A. E.: Birdshot retinochoroidopathy associated with HLA-A29 antigen and immune responsiveness to retinal S-antigen. Am. J. Ophthalmol. 94:147, 1982.

13. Priem, H. A., De Rouck, A., De Laey, J.-J., and Bird, A. C.: Electrophysiologic studies in birdshot chorioretinopathy. Am. J. Ophthalmol. 106:430, 1988.

14. Priem, H. A., Kijlstra, A., Noens, L., Baarsma, G. S., De Laey, J. J., and Oosterhuis, J. A.: HLA typing in birdshot chorioretinopathy. Am. J. Ophthalmol. 105:182, 1988.

Choroidal Perfusion Abnormality With Age-Related Bruch's Membrane Change

D. Pauleikhoff, M.D., J. C. Chen, M.D., I. H. Chisholm, M.B.B.S., and A. C. Bird, M.D.

Observation of patients with Sorsby's fundus dystrophy has shown that a prolonged choroidal filling phase on fluorescein angiography may indicate the presence of diffuse thickening of Bruch's membrane. We analyzed fluorescein angiography transit photographs in 100 eyes of 100 consecutive patients with age-related changes at the level of Bruch's membrane. Of these, 26 eyes had evidence of a prolonged choroidal filling phase during the initial dye transit. We suggest that this may represent a clinical correlate of diffuse thickening of Bruch's membrane, and that the two features are causally related.

AGE-RELATED MACULAR DISEASE is now the most common cause of registerable blindness in Western countries.[1-4] It is believed that deposits of abnormal material in Bruch's membrane are important in the pathogenesis of those lesions causing loss of central vision.[5,6] Age-related macular disease is a progressive phenomenon, although variation exists between individuals. The changes may be detected by microscopy in an individual as early as 10 years of age, and are seen consistently by the age of 60 years.[7-10]

The abnormal deposits are believed to be derived from the retinal pigment epithelium.[10-14] There is evidence that the pigment epithelial cells continuously discharge cytoplasmic material into the inner portion of Bruch's membrane by apoptosis.[15-18] By this mechanism, it is believed that the pigment epithelium voids the products of phagosomal degradation and other metabolic activities. It is thought that the discharged material subsequently diffuses through Bruch's membrane and is cleared by the choroidal capillaries. Accumulation of debris in Bruch's membrane results from failure to clear the cytoplasmic contents deposited in this region.

Microscopic studies show that thickening of Bruch's membrane may be in the form of discrete deposits on its inner surface, or diffuse (linear) accumulation, which is seen as a continuous layer in the inner or outer portion of Bruch's membrane. This thickening may be compounded by excessive basement membrane production by pigment epithelium.[8,19] There is associated reduction of the cross-sectional area of the choriocapillaris,[20,21] and in one flat preparation of the inner choroid, the normal pattern of sinusoidal capillaries had been replaced by a tubular system.[22]

Clinical studies have been directed toward the analysis of discrete deposits on the inner surface of Bruch's membrane alone, which are recognized ophthalmoscopically as drusen. Because of a lack of clinical correlates, however, the potential importance of diffuse changes affecting the inner and outer aspect of Bruch's membrane and alteration of the inner choroid have been largely ignored.

As a result of studies on Sorsby's fundus dystrophy,[23-25] it has been suggested that a prolonged choroidal filling phase on fluorescein angiography may be a clinical sign of diffuse thickening of Bruch's membrane. In this autosomal dominant condition, a continuous layer of abnormal material up to 30 μm thick is deposited between the inner collagenous layer of Bruch's membrane and the basement membrane of the retinal pigment epithelium.[26] In contrast with the normal rapid filling, a contiguous area of prolonged, patchy choroidal fluorescence is seen during the transit phase of the

Accepted for publication Oct. 24, 1989.
From the Department of Clinical Ophthalmology, Institute of Ophthalmology, London, England. This study was supported by the Deutsche Forschungsgemeinschaft (Dr. Pauleikhoff); a fellowship from the McLaughlin Foundation, Canada (Dr. Chen); and by Medical Research Council grant No. G 8709312 N.
Reprint requests to A. C. Bird, M.D., Institute of Ophthalmology, Moorfields Eye Hospital, City Road, London, England EC1 2PD.

angiogram.[23-25] Major choroidal blood vessels are seen before filling of the choriocapillaris. The dye appears initially in the inner choroid as small points of fluorescence, which gradually enlarge and coalesce over several frames of the angiogram. Continuous fluorescence indistinguishable from the surrounding normal fundus is not apparent until the venous phase of the retinal circulation. This appearance is similar to that seen in experimental ocular hypertension,[27] and is compatible with concepts derived from observations of animals and humans.[28-41] The criteria used in this study for the detection of deranged perfusion were derived from the observations of patients with known choroidal vascular disease.[36,41,42]

Material and Methods

The presence of a prolonged choroidal filling phase was evaluated by angiography in 100 consecutive patients in a prospective study of age-related macular degeneration. All patients were over 60 years of age and showed signs of age-related changes consisting of drusen in both eyes, or pigment epithelial detachment or choroidal neovascular membranes in one eye and drusen in the other. Color fundus photographs and fluorescein angiograms were undertaken on each patient. Only those eyes with adequate early transit phase of the angiogram were included in the study. This was considered acceptable in one eye of a patient with bilateral drusen, the fellow eye of one with unilateral exudative disease, or, in a small number of patients, in an eye with limited subretinal neovascularization in an area of the macula without detectable subretinal fluid. One hundred eyes of 100 patients satisfied these criteria out of the first 115 consecutive patients incorporated into a prospective study. These 100 eyes were analyzed.

A prolonged choroidal filling phase was defined as a contiguous area of prolonged, patchy choroidal fluorescence in the transit phase of the fluorescein angiogram extending over at least five disk areas. In each patient, the major choroidal blood vessels were seen before filling of the choriocapillaris. The dye appeared initially in the inner choroid as small points of fluorescence, which gradually enlarged and coalesced over several frames of the angiogram. Continuous fluorescence indistinguishable from the surrounding normal fundus was not seen until the venous phase of the retinal circulation (Figs. 1 and 2).

Correlation was sought between the presence or absence of choroidal perfusion deficit and the state of the macula in the fellow eye, and with drusen characteristics in the study eye. Drusen were characterized according to a previously described method.[42] Drusen were analyzed inside a circle 1,600 μm from the fovea and between 1,600 μm and 2,400 μm from the foveola. They were classified by number (<10, 10 to 20, >20), size (<50 μm, 50 to 500 μm, >500 μm), density (scattered, subconfluent, confluent), and early and late angiographic behavior (equal to choroidal fluorescence, slightly brighter than choroidal fluorescence, brightly fluorescent). Good reproducibility has been shown for this technique.[43] The distribution of drusen was compared in the two groups using chi-square test of statistical significance. A P-value of less than .01 was taken to indicate a significant difference.

Results

Of the 100 eyes studied, the angiographic characteristics of prolonged choroidal filling

TABLE 1
CHOROIDAL FILLING BY SEX AND AGE

	CHOROIDAL FILLING PHASE	
	PROLONGED	NOT PROLONGED
Men	44.4%	41.1%
Women	55.6%	58.9%
Mean age (yrs)	70.4	68.9
Age range (yrs)	53–81	50–88

TABLE 2
CHANGES IN THE FELLOW EYE

	CHOROIDAL FILLING PHASE	
	PROLONGED	NOT PROLONGED
Drusen	5 (19.3%)	18 (24.3%)
Occult new vessels	3 (11.5%)	9 (12.2%)
Disciform lesion	18 (69.2%)	47 (63.5%)

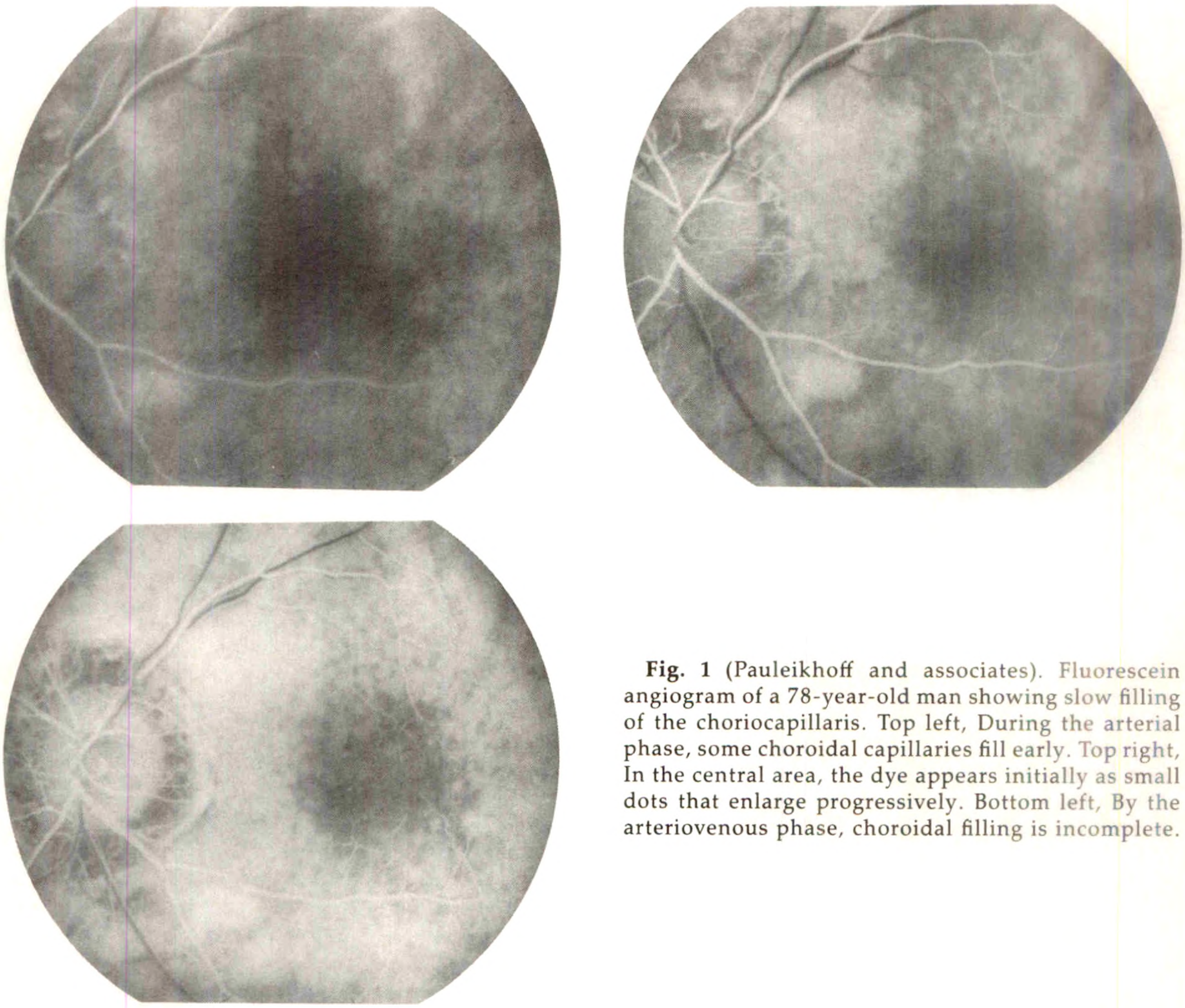


Fig. 1 (Pauleikhoff and associates). Fluorescein angiogram of a 78-year-old man showing slow filling of the choriocapillaris. Top left, During the arterial phase, some choroidal capillaries fill early. Top right, In the central area, the dye appears initially as small dots that enlarge progressively. Bottom left, By the arteriovenous phase, choroidal filling is incomplete.

phase were identified in 26 eyes. In 74 eyes, choroidal filling was normal. The sex and age distributions in the two groups were similar (Table 1). The fundus lesions in the fellow eye in the two groups were also similar (Table 2). Comparison of drusen characteristics between both groups demonstrated a significant difference in the number and density of drusen in the central macula (Tables 3 and 4). Eyes with abnormal choroidal filling tend to have fewer drusen, and the drusen were less densely distributed in the central region than they were in eyes with a normal angiographic appearance. There were no significant differences in the size and fluorescence of drusen or their density or number in the peripheral macula.

Discussion

The results of this study suggest that the angiographic appearance of choroidal perfusion is modified in some patients with age-related macular degeneration. This angiographic sign could represent the clinical correlate of changes in the choriocapillaris as identified by microscopy.[20-22] It cannot be assumed, however, that the angiographic appearance implies perfusion deficit alone, because it may also be modified by the accumulated material in Bruch's membrane. Although the initial choroidal fluorescence is likely to be derived from the

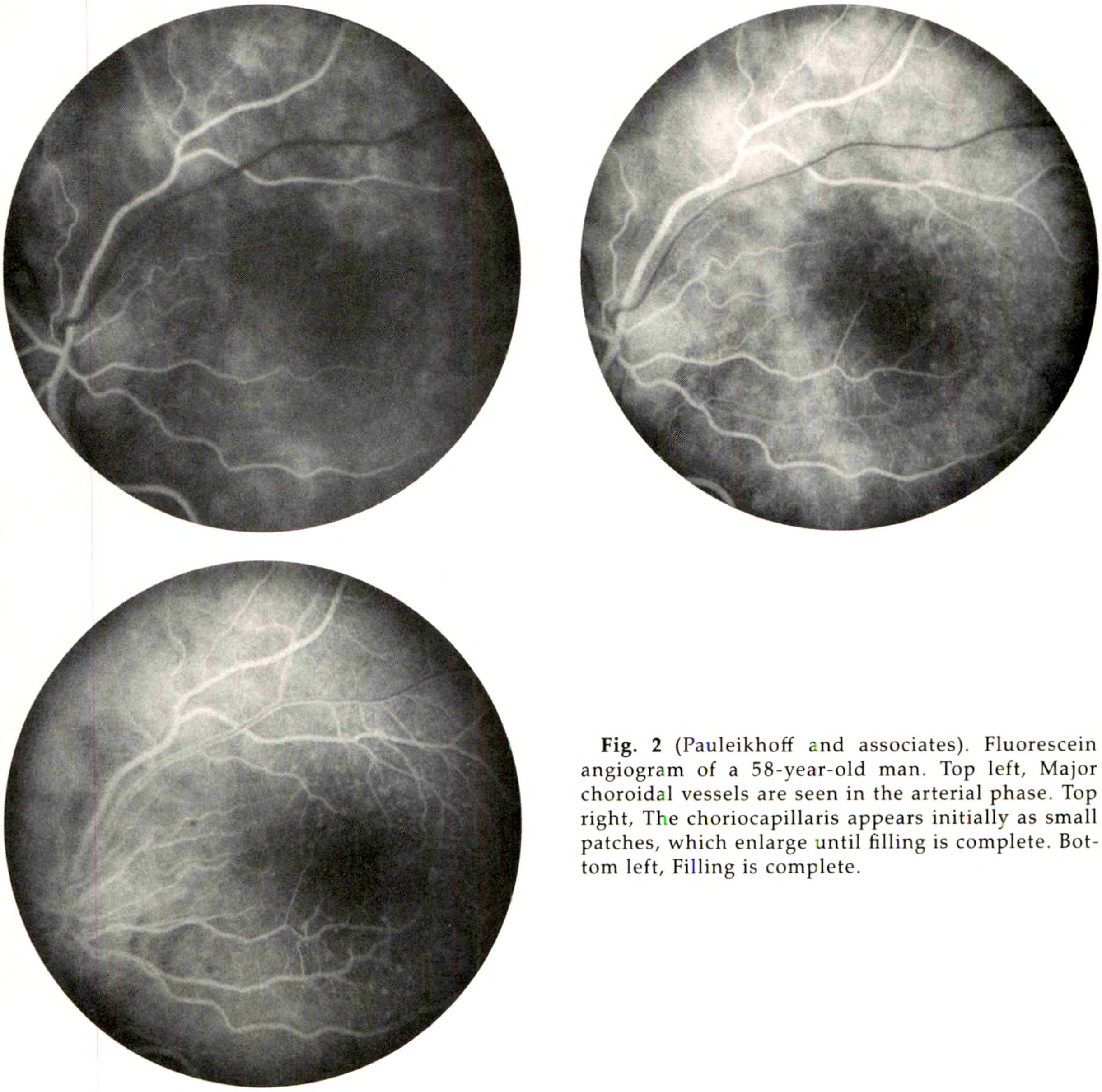


Fig. 2 (Pauleikhoff and associates). Fluorescein angiogram of a 58-year-old man. Top left, Major choroidal vessels are seen in the arterial phase. Top right, The choriocapillaris appears initially as small patches, which enlarge until filling is complete. Bottom left, Filling is complete.

dye in the choroidal blood vessels and extracellular space of the choroid, the subsequent distribution of fluorescein has not been well-defined, particularly in disease. Fluorescence microscopy shows the dye to be in Bruch's membrane and some drusen rather than in the extracellular space of the choroid soon after injection.[44] It is likely that the dye is bound to extracellular polar molecules. If this is the case, choroidal fluorescence would be modified by changes in the speed of effusion of dye from the choroidal capillaries, the diffusion characteristics of abnormal deposits, and the binding properties of Bruch's membrane.

There may be a causal relationship between the prolonged filling phase and diffuse thickening of Bruch's membrane. It is not possible to determine whether the changes are initiated by alteration of the choroidal capillaries or by deposition of abnormal material. The sequence of events may be initiated by abnormality of the choriocapillaris, thereby reducing diffusion into the intravascular space of waste material derived from the retinal pigment epithelial

TABLE 3

NUMBER OF DRUSEN IN THE CENTRAL MACULA*

	CHOROIDAL FILLING PHASE	
	PROLONGED	NOT PROLONGED
<10	30.8%	12.2%
10–20	3.8%	6.8%
>20	65.4%	81.1%

*The number of drusen in the two groups is significantly different ($P < .005$).

TABLE 4

DENSITY OF DRUSEN IN THE CENTRAL MACULA*

	CHOROIDAL FILLING PHASE	
	PROLONGED	NOT PROLONGED
Scattered	26.9%	16.2%
Subconfluent	73.1%	52.7%
Confluent	0%	31.1%

*The density of drusen in the two groups is significantly different ($P = .005$).

cells. Thus, the debris would not be cleared and would collect in the outer part of Bruch's membrane. The alternative explanation that diffuse deposits may induce secondary changes of the choroidal capillaries has been proposed in the context of Sorsby's fundus dystrophy.[26] There is evidence that the retinal pigment epithelium regulates the choroidal capillaries,[45,46] and mechanisms by which this regulation may occur have been defined.[47-49] If the normal functional attributes of the choriocapillaris are dependent on the presence of diffusible factors derived from the pigment epithelium, a diffusion barrier between the two cell systems would cause secondary change in the choroid. The degree of diffusion block would depend on both the quantity and chemical constitution of the deposits. That physical displacement of the capillaries by the deposits is a possible contributory factor is undeniable. Such a mechanism, however, is not essential, because in Sorsby's fundus dystrophy the deposits are internal to the inner collagenous layer of Bruch's membrane.[26]

The potential effect of these abnormalities on metabolic processes has yet to be determined. That deposits in the outer part of Bruch's membrane and choroid may hamper metabolic exchange between the choroidal capillaries and the pigment epithelium cannot be discounted,[9] particularly if the debris contained neutral fats.[50] This could account for diffuse loss of scotopic function associated with age-related macular disease.[51] It would also explain the negative correlation of drusen and diffuse deposits,[10] and the relative scarcity of drusen in patients with slow choroidal filling, as identified in this study, if the quantity of material discharged into Bruch's membrane is related to metabolic activity.

Although the evidence associating the angiographic abnormality and diffuse deposits is circumstantial, the association explains certain observations that have been unexplained to date, and the hypothesis is amenable to further investigation by clinical and histopathologic studies.

ACKNOWLEDGMENT

Statistical analyses were performed by Darwin Minassian, M.Sc., Department of Preventative Ophthalmology, Institute of Ophthalmology, London, England.

References

1. Sorsby, A.: Reports on Public Health and Medical Subjects. London, HMSO, 1966.
2. Kahn, H. A., and Moorhead, H. B.: Statistics on Blindness in the Model Reporting Areas 1969–70. United States Department of Health, Education, and Welfare Publication No. (NIH) 73-427. Washington, D.C., U.S. Government Printing Office, 1973.
3. Leibowitz, H., Krueger, D. E., Maunder L. R., Milton, R. C., Kini, M. M., Khan, H. A., Mickerson, R. J., Pool, J., Colton, T. L., Ganley, J. P., Loewenstein, J. I., and Dawber, T. R.: The Framingham Eye Study Monograph. An ophthalmological and epidemiological study of cataract, glaucoma, diabetic retinopathy, macular degeneration and visual acuity in a general population of 2,631 adults, 1973–75. Surv. Ophthalmol. 25(suppl.):335, 1984.
4. Ghafour, M., Allan, D., and Foulds, W. S.: Common causes of blindness and visual handicap in the West of Scotland. Br. J. Ophthalmol. 67:209, 1983.
5. Gass, J. D. M.: Pathogenesis of disciform detachment of the neuroepithelium. III. Senile disciform macular degeneration. Am. J. Ophthalmol. 63:617, 1967.
6.———: Drusen and disciform macular detachment and degeneration. Arch. Ophthalmol. 90:206, 1973.
7. Hogan, M. J., and Alvarado, J.: Studies on the

human macula. IV. Aging changes in Bruch's membrane. Arch. Ophthalmol. 77:410, 1967.
8. Sarks, S. H.: Aging and degeneration in the macular region. A clinico-pathological study. Br. J. Ophthalmol. 60:324, 1967.
9. Green, W. R., and Key, S. N.: Senile macular degeneration. A histopathological study. Trans. Am. Ophthalmol. Soc. 75:180, 1977.
10. Feeney-Burns, L., and Ellersieck, M. R.: Age-related changes in the ultrastructure of Bruch's membrane. Am. J. Ophthalmol. 100:686, 1985.
11. Farkas, T. G., Sylvester, V., and Archer, D.: The ultrastructure of drusen. Am. J. Ophthalmol. 71:1196, 1971.
12. Farkas, T. G., Sylvester, V., Archer, D., and Altona, M.: The histochemistry of drusen. Am. J. Ophthalmol. 71:1206, 1971.
13. Hogan, M. J.: Role of the retinal pigment epithelium in macular disease. Trans. Am. Acad. Otolaryngol. Ophthalmol. 7:4, 1972.
14. Grindle, C. F. J., and Marshall, J.: Aging changes in Bruch's membrane and their functional implications. Trans. Ophthalmol. Soc. U.K. 98:172, 1978.
15. Reme, C.: Autophagy in visual cells and pigment epithelium. Invest. Ophthalmol. 16:807, 1977.
16. Rungger-Branche, E., Englert, U., and Leuenberger, P. M.: Exocytic clearing of degraded membrane material from pigment epithelial cells in frog retina. Invest. Ophthalmol. Vis. Sci. 28:2026, 1986.
17. Burns, R. P., and Feeney-Burns, L.: Clinico-morphological correlations of drusen and Bruch's membrane. Trans. Am. Ophthalmol. Soc. 78:206, 1980.
18. Ishibashi, T., Sorgente, N., Patterson, R., and Ryan, S. J.: Pathogenesis of drusen in the primate. Invest. Ophthalmol. Vis. Sci. 27:184, 1986.
19. Loffler, K. U., and Lee, W. R.: Basal linear deposits in the human macula. Graefes Arch. Ophthalmol. 224:493, 1986.
20. Sarks, S. H.: Changes in the region of the choriocapillaris in aging and degeneration. XXIII Concilium Ophthalmologicum, Kyoto, 1978. Amsterdam, Excerpta Medica, 1978, pp. 228–238.
21. Sarks, S. H., Sarks, J., and Killingsworth, C.: Evolution of geographic atrophy of the retinal pigment epithelium. Eye 2:552, 1988.
22. Tso, M. O. M.: Pathogenetic factors of aging macular degeneration. Ophthalmology 92:628, 1985.
23. Hoskin, A., Sehmi, K., and Bird, A. C.: Sorsby's pseudo-inflammatory macular dystrophy. Br. J. Ophthalmol 65:859, 1981.
24. Capon, M., Polkinghorne, P., and Bird, A. C.: Sorsby's pseudo-inflammatory dystrophy. Sorsby's fundus dystrophy. Eye 2:114, 1988.
25. Polkinghorne, P. J., Capon, M. R., Berninger, T. A., Lyness, A. L., Sehmi, K., and Bird, A. C.: Sorsby's fundus dystrophy. A clinical study. Ophthalmology. In press.
26. Capon, M. R. C., Marshall, J., Kraft, J. I., Alexander, R. A., Hiscott, P. S., and Bird, A. C.: Sorsby's fundus dystrophy. A light and electron microscopic study. Ophthalmology. In press.
27. Dollery, C. T., Henkind, P., Kohner, E. M., and Paterson, J. W.: Effect of raised intraocular pressure on the retinal and choroidal circulation. Invest. Ophthalmol. Vis. Sci. 7:191, 1968.
28. Hayreh, S. S.: Recent advances in fluorescein fundus angiography. Br. J. Ophthalmol. 58:391, 1974.
29. Shimizu, K.: Segmental nature of angioarchitecture of the choroid. In Shimizu, K., and Oosterhuis, J. A. (eds.): Ophthalmology. Amsterdam, Excerpta Medica, 1979, pp. 215–219.
30. Torczynski, E., and Tso, M. O. M.: The architecture of the choriocapillaris at the posterior pole. Am. J. Ophthalmol. 81:428, 1976.
31. Yoneya, S., and Tso, M. O. M.: Angioarchitecture of the human choroid. Arch. Ophthalmol. 105:681, 1987.
32. Hayreh, S. S., and Baines, J. A. B.: Occlusion of the posterior ciliary artery. I. Effects on choroidal circulation. Br. J. Ophthalmol. 56:719, 1972.
33. Hayreh, S. S., and Baines, J. A. B.: Occlusion of the posterior ciliary artery. II. Chorio-retinal lesions. Br. J. Ophthalmol. 56:736, 1972.
34. Stern, W. H., and Ernest, J. T.: Microsphere occlusion of the choriocapillaris in rhesus monkeys. Am. J. Ophthalmol. 78:438, 1974.
35. Cogan, D. G.: Ocular involvement in disseminated intravascular coagulopathy. Arch. Ophthalmol. 93:1, 1975.
36. Friedman, E., Smith, T. R., Kuwabara, T., and Beyer, C. K.: Choroidal vascular patterns in hypertension. Arch. Ophthalmol. 71:842, 1964.
37. Gaudric, A., Coscas, G., and Bird, A. C.: Choroidal ischemia. Am. J. Ophthalmol. 94:489, 1982.
38. Gitter, K. A., Houser, B. P., Sarin, L. K., and Justice, J., Jr.: Toxemia of pregnancy. An angiographic interpretation of fundus changes. Arch. Ophthalmol. 80:449, 1968.
39. Klien, B. A.: Ischemic infarcts of the choroid (Elschnig spots). A cause of retinal separation in hypertensive disease with renal insufficiency. A clinical and histopathologic study. Am. J. Ophthalmol. 66:1069, 1968.
40. Young, N. J. A., Bird, A. C., and Sehmi, K.: Pigment epithelial diseases with abnormal choroidal perfusion. Am. J. Ophthalmol. 90:607, 1980.
41. Van Buskirk, E. M., Lessell, S., and Friedman, E.: Pigment epitheliopathy and erythema nodosum. Arch. Ophthalmol. 85:369, 1971.
42. Chuang, E. L., and Bird, A. C.: The pathogenesis of tears of the retinal pigment epithelium. Am. J. Ophthalmol. 105:285, 1988.
43. Barondes, M. J., Pauleikhoff, D., Chisholm, I. H., Minassian, D., and Bird, A. C.: Bilaterality of drusen. Br. J. Ophthalmol. In press.

44. Bird, A. C., and Marshall, J.: Retinal pigment epithelial detachments in the elderly. Trans. Ophthalmol. Soc. U.K. 105:674, 1986.
45. Henkind, P., and Gartner, S.: The relationship between retinal pigment epithelium and the choriocapillaris. Trans. Ophthalmol. Soc. U.K. 103:444, 1983.
46. Korte, G. E., Repucci, V., and Henkind, P.: RPE destruction causes choriocapillary atrophy. Invest. Ophthalmol. Vis. Sci. 25:1135, 1984.
47. Glaser, B. M., Campochiaro, P. A., Davies, J. L., and Sato, M.: Retinal pigment epithelial cells release an inhibitor of neovascularization. Arch. Ophthalmol. 103:1870, 1985.
48. Pollack, A., Korte, G. E., Weitzner, A. L., and Henkind, P.: Ultrastructure of Bruch's membrane after laser krypton photocoagulation. I. Breakdown of Bruch's membrane. Arch. Ophthalmol. 104:1372, 1986.
49. Pollack, A., Korte, G. E., Heriot, W. J., and Henkind, P.: Ultrastructure of Bruch's membrane after laser krypton photocoagulation. II. Repair of Bruch's membrane and the role of macrophages. Arch. Ophthalmol. 104:1377, 1986.
50. Pauleikhoff, D., Marshall, J., and Bird, A. C.: Histochemical and morphological correlation of aging changes in Bruch's membrane. Invest. Ophthalmol. Vis. Sci. 30(suppl.):153, 1989.
51. Sunness, J. S., Johnson, M. A., Massoff, R. W., and Marcus, S.: Retinal sensitivity over drusen and nondrusen areas. A study using fundus perimetry. Arch. Ophthalmol. 96:375, 1989.

OPHTHALMIC MINIATURE

The larger the type size, the more leading is required to prevent the eye from being distracted by the lines above and below the one being read. Also, the wider the line of type, the greater the leading needed, because the eye in moving from the end of one line to the beginning of the next takes a long jump, and in closely set material the eye may easily jump to the wrong line.

The Chicago Manual of Style, 13th edition
Chicago, University of Chicago Press, 1982, p. 568

Refinements in Microinstrumentation for Vitreous Surgery

Eugene de Juan, Jr., M.D., and Dyson Hickingbotham

We developed a series of 25-gauge (0.5 mm) microinstruments for vitreous surgery, including a 25-gauge vitreous cutter, 25-gauge microscissors for limited reuse, and a vitreous membrane dissector. Clinical experience with these instruments in more than 20 cases of advanced proliferative vitreoretinopathy, retinopathy of prematurity, and diabetic retinopathy indicates that these instruments facilitate delicate vitreoretinal dissections, particularly in the vitreous base and when fibrovascular tissues are closely adherent to the retina. Because of their smaller size, the microinstruments are more precise in their cutting capabilities than other instruments.

Since the introduction of the first clinically useful vitreous cutter in 1971 by Machemer and associates,[1] there have been improvements in instruments for vitreous surgery. One important change that has occurred has been the reduction in the size of the vitreous cutters. Machemer's early instrument was 1.7 mm in diameter without the fiberoptic sleeve and 2.3 mm with the fiberoptic sleeve. This multifunction probe was gradually replaced by the lighter and smaller pneumatically driven 20-gauge (0.9 mm) cutters.[2] Because of improvements in control of aspiration[3] and quality control in the manufacture, these cutters have served well over the past ten years. As surgeons became more demanding about the removal of scarred vitreous in the vitreous base[4,5] and in infant eyes,[6,7] the vitreous cutters appeared to be too large and seemed to cut too coarsely.

To overcome shortcomings in the existing instruments, we developed a series of microinstruments based on a 25-gauge (0.5 mm) system. These include a 25-gauge guillotine vitreous cutter, 25-gauge pneumatically driven scissors, and a vitreous membrane dissector. Clinical experience in more than 20 cases indicates that these instruments facilitate delicate vitreoretinal dissections and, because of their smaller size, are more precise in their cutting capabilities.

Accepted for publication Nov. 28, 1989.

From the Duke University Eye Center, Durham, North Carolina. This work was supported in part by Research to Prevent Blindness, Inc., New York, New York. Duke University will receive royalties based on the sale of the microinstruments described herein; however, the authors will receive no direct compensation.

Reprint requests to Eugene de Juan, Jr., M.D., Box 3802, Duke University Eye Center, Duke University, Durham, NC 27710.

Material and Methods

The 25-gauge cutter is a pneumatically driven guillotine cutter that uses a disposable vitreous cutter mechanism. The outer tube diameter near the tip is 0.5 mm. The tube is thin-walled to allow maximum aspiration. There is a 0.45-mm port opening 0.3 mm from the tip. The tube widens to a 20-gauge size (0.9 mm) 10 mm from the tip (Fig. 1), which facilitates aspiration and prevents plugging.

The 25-gauge scissors are driven pneumatically, as is the vitreous cutter. The tip is shaped to facilitate dissections of preretinal membranes without causing retinal injury (Fig. 2).

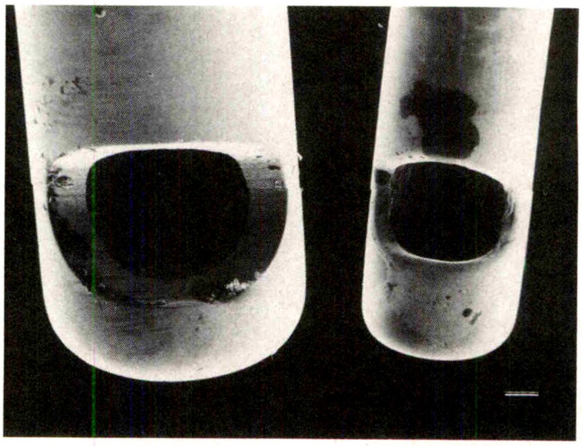


Fig. 1 (de Juan and Hickingbotham). Left, Standard 20-gauge (0.9-mm diameter) instrument. Right, 25-gauge (0.5-mm diameter) vitreous cutter. Bar, 100 µm.

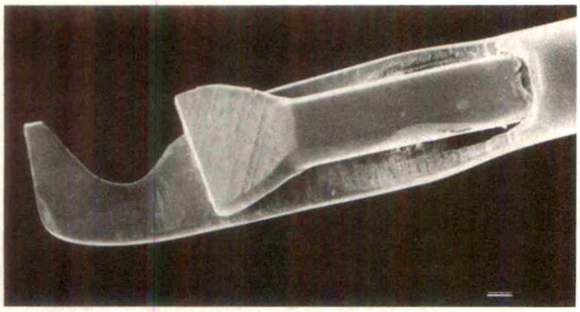


Fig. 2 (de Juan and Hickingbotham). Scanning electron micrograph of 25-gauge microscissors. Bar, 100 μm.

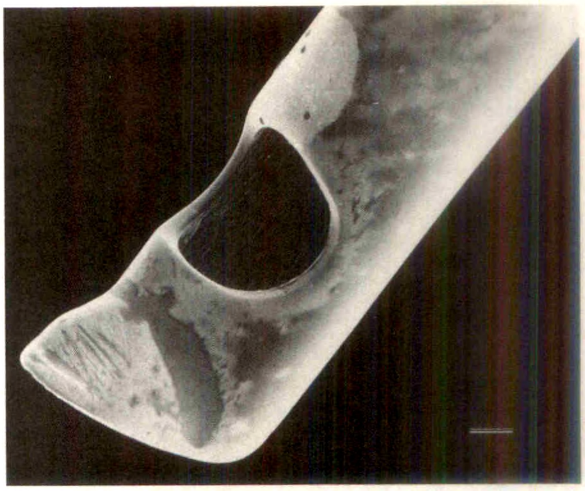


Fig. 3 (de Juan and Hickingbotham). Micrograph of 25-gauge vitreous and membrane dissector. Tip of cutter is shaped to facilitate identification and dissection of tissue planes. The tip also prevents underlying tissue, such as retina, from entering the port. Bar, 100 μm.

Because they are designed for limited reuse, the scissors can be discarded when they become dull, which prevents waiting for repairs.

The dissector combines the functions of a vitreous cutter and microscissors. The dissector combines the 25-gauge guillotine cutter with a special tip that acts as a dissecting pick and directs the tissue being cut into the mouth of the cutter (Fig. 3). With this instrument, membranes on the surface of the retina can be lifted slightly and fed into the cutter and removed in a single step. The small tip also prevents the retina and other unwanted structures from being inadvertently aspirated and cut.

Discussion

The 25-gauge vitreous cutter does not replace the regular cutters to remove the central vitreous. The removal of the vitreous with the 25-gauge cutter is slow compared with the 19- or 20-gauge instruments currently available. Consequently, the smaller cutter is not needed or even desired in many cases. Its real advantages, however, become apparent when debulking the vitreous base in proliferative vitreoretinopathy is needed or during delicate dissections in surgery for retinopathy of prematurity. In these cases, precise cuts must be made close to the retinal surface, but the retina must be avoided to prevent an unplanned retinal hole. The 25-gauge instrument performs this task well because the retina does not tend to enter the port of the cutter. Because the cutter has a small internal diameter, it can become clogged when lens material or fibrous tissue is aspirated. Blockages can be removed by backflushing the line.

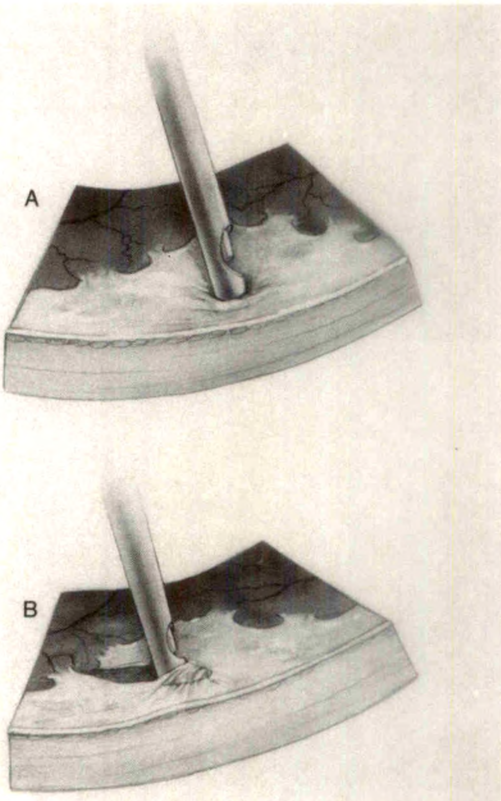


Fig. 4 (de Juan and Hickingbotham). Relative advantage of dissector (B) for removing tissue close to the retinal surface is shown.

The 25-gauge microscissors are easy to handle and can be used in place of other vertically acting scissors. Their main advantages are their small size and simple design.

The vitreous membrane dissector has distinct advantages over other cutting techniques in some complex (and simple) cases of retinopathy of prematurity and diabetic proliferative disease. In these cases, the small pic at the tip of the cutter allows one to engage a membrane close to the retinal surface, lift it up (such as a blade of a scissors would), and remove the tissue by a combination of cutting and aspiration (Fig. 4). This procedure removes the dissected tissue rapidly and increases visualization. The small pic also prevents the retina from inadvertent aspiration into the port.

When these microinstruments are combined with instruments like the fiberoptic forceps,[5] they are effective in detaching a fibrous and adherent posterior hyaloid face in patients with proliferative diabetic retinopathy or removing the vitreous proliferations in retinopathy of prematurity.

References

1. Machemer, R., Buettner, H., and Norton, E. W. D.: Vitrectomy. A pars plana approach. Ophthalmology (Rochester) 75:OP 813, 1971.
2. O'Malley, C., and Heintz, R. M., Sr.: Vitrectomy with an alternative instrument system. Ann. Ophthalmol. 7:585, 1975.
3. Charles, S., and Wang, C.: A linear suction control for vitreous surgery. Arch. Ophthalmol. 99:1613, 1980.
4. Aaberg, T. M.: Management of anterior and posterior proliferative vitreoretinopathy. XLV Edward Jackson memorial lecture. Am. J. Ophthalmol. 106:519, 1988.
5. De Juan, E., Jr., and McCuen, B., II: Management of anterior vitreous traction in proliferative vitreoretinopathy. Retina. In press.
6. Trese, M.: Two-hand dissection technique during closed vitrectomy for retinopathy of prematurity. Am. J. Ophthalmol. 101:251, 1986.
7. De Juan, E., Jr., and Machemer, R.: Retinopathy of prematurity. Surgical technique. Retina 7:63, 1987.

AMERICAN JOURNAL OF OPHTHALMOLOGY®

FRANK W. NEWELL, *Publisher and Editor-in-Chief*
Suite 1415, 435 North Michigan Ave., Chicago, Illinois 60611

Published monthly by the OPHTHALMIC PUBLISHING COMPANY
Suite 1415, 435 North Michigan Avenue, Chicago, Illinois 60611

EDITORIAL

Peer Review

Frank W. Newell

Peer: (1) An equal in civil standing or rank; one's equal before the law; (2) one who takes rank with another in point of natural gifts or other qualifications; an equal in any respect; (3) one who is associated or matched with another, a companion, mate, a rival.

Review: (2) The act of looking over something with a view to correction or improvement; a revision of a book (an article, etc). Now rare. (7) A general account or criticism of a literary work (especially a new or recent one) either published separately or, more usually, as an article in a periodical or newspaper.

Peer review has become the sine qua non of medical and scientific publishing. Authors speak of having published in peer review journals. Some universities and learned societies require publication in peer review journals for promotion or membership. The publications that qualify as having peer review are not defined. The term is mainly used as a synonym for excellence in journals that are distributed through paid subscription or as a perquisite of membership in a professional association. No journal advertises itself as having peer review, although the instructions to authors often indicate that all material submitted has outside review before publication. Readers generally assume that the original articles published in the top notch professional journals have been reviewed and recommended for publication by experts other than the members of the editorial board. Not all material in a journal, however distinguished, necessarily undergoes outside review. Editorials, book reviews, solicited and special articles, letters to the editor, corrections, and news items are usually managed internally.

Every article submitted to a journal does not have outside review. The review process is so demanding and time consuming that a decision may be made to reject a submission to the author without review. The mechanical preparation of such papers may be so faulty that the editor cannot judge the quality of the ideas. The paper may deal with a topic too complex,

too simple, or outside of the scope of the publication. The proportion of material submitted that is returned without outside review is not known but many journals that have a high rejection rate may return most typescripts without outside review.

Some years ago The Journal asked that each reviewer answer a number of questions concerning each article:

Is the subject matter original, important, and novel enough to justify publication in The Journal?

Is the topic suitable for the readership of The Journal?

Is the paper well organized and is it easy to read?

Is the overall quality of the work in the top 25 percent in the field?

Are adequate details of examination and diagnostic procedures described for any disorder or disease ?

Are the source and selection of the subjects adequately described?

Are all of the subjects accounted for in a data analysis?

Are any experimental methods or surgical procedures described in sufficient detail that the study may be repeated?

Are the scientific methods sound?

Are the statistical methods appropriate and do they justify the conclusions?

Is each table properly titled and numbered? Does each table properly augment the text, or does it duplicate material already described in the text? Are the data presented accurately?

Are the references accurate? Do the references refer specifically to the topic studied? Are there too many, too few, or too many from a single source? Are the references prepared in the style used by The Journal?

Do the illustrations complement the article? Are they likely to reproduce well?

Are the legends prepared in The Journal style? Do they adequately and succinctly explain the figures?

If the referees answer each question affirmatively the article is likely to be recommended for publication. But then two main questions arise: (1) the suitability of the topic for publication in The Journal and (2) the effort required to prepare the material for publication. The originality and timeliness of the topic involve a number of factors not always obvious to the contributor or reviewer. Research, however outstanding, if without obvious clinical relevance may be more suitable for a basic science journal. Case reports that describe a single patient are often more suited to the Letters section. Sometimes articles are awaiting publication that deal with the same topic and duplication is not desirable.

Preparation of the material for publishing mainly concerns the author's attention to the Instructions to Authors that are printed frequently. Double-spacing of typescripts is the rule posted in every writing class, yet, a surprising number of typescripts are submitted with single-spaced references, quotations, or title pages. Many authors prefer abbreviations or initials although The Journal abbreviates only units of measurement. Inaccurate references may disqualify a typescript. Exact measurements must be given and not subjective data. Numbers must be provided with percentages in parentheses where appropriate. Percentages without numbers are never adequate. Enough information must be provided so that the reader will know what was done.

The Journal attempts to be certain that all authors submitting a paper have participated in the study by having them sign the disclosure statement, "The authors of this study confirm that each has contributed significantly to the formulation and execution of the study and the writing of the paper. The authors further confirm that they have read and concur in the writing and conclusion of the typescript, data, and illustrations submitted therein." Some of the startling instances of fraud in the recent decade have occurred in the laboratories of renowned investigators in which it appears that the famed author provided long-distance supervision and was so distant from the study as to not know the details of studies conducted in their own laboratories or clinics. Editors learn that some established investigators submit material that they have not read. Some individuals apparently permit their name to be attached to typescripts so that the editor, and not themselves will bear the onus of rejection.

Contributors sometimes request that their papers not be reviewed by particular authorities and the editor of The Journal complies. Conversely some authors have channeled suggestions through members of the editorial board that the authors are so distinguished that outside review (or even editorial correction) is not required.

Scientific referees are essential to the peer review process. In a field that encompasses as many different disciplines as ophthalmology, no individual can be familiar with all of its

aspects. The reader has a right to assume that the articles are medically and scientifically sound and have been reviewed by experts in the field. Authors should be assured that the decision to accept or reject does not reflect special interests.

With the emphasis in the past decade upon fraud in publishing, all too often mention of peer review stimulates a discussion of fraud in science. This is a pity for the purpose of peer review is not to ferret out fraud. Indeed, there is usually no way in which the reviewer or editor can determine if a study is valid or fabricated. Purely and simply, the reviewer advises the editor, not the authors, concerning the suitability of material for publication.

The contribution of the referee cannot be overestimated. In many instances the referee provides a more current or pertinent understanding of a topic than that given in the paper. Sometimes it is evident that more thought has gone into the review than into the original paper. Referees labor long and anonymously. Their only reward is that medicine and its publications are richer for the effort.

Sometimes disappointed authors guess that a particular member of the editorial board is responsible for an unfavorable review or rejection of their typescript. Mainly their guesses are wrong. Many papers with favorable reviews are so technical or so distant from clinically applicable material that they are rejected by the editor. Other papers that have an initially unfavorable review may be accepted for publication after revision.

LETTERS TO THE JOURNAL

Subretinal Neovascularization After Operating Microscope Burn

Nicholas J. Leonardy, M.D., Charles K. Dabbs, M.D., and Paul Sternberg, Jr., M.D.

Department of Ophthalmology, Emory University School of Medicine. Supported in part by a departmental grant from Research to Prevent Blindness, Inc., and by a departmental core grant, P30 EY06360, from the National Institutes of Health.

Inquiries to Paul Sternberg, Jr., M.D., Emory University School of Medicine, 1327 Clifton Rd. N.E., Atlanta, GA 30322.

Light-induced retinal injury caused by the operating microscope has been recognized as a complication of intraocular surgery.[1] Visual deficits caused by this mechanism frequently improve in the first few months after the injury.[2] We examined a patient with late onset of postoperative visual changes caused by a subretinal neovascular membrane developing at the edge of an operating microscope burn.

A 71-year-old man had an acute onset of metamorphopsia in the left eye. Eighteen months earlier, the patient had an extracapsular cataract extraction with a posterior chamber intraocular lens implant in the left eye. Preoperative fundus examination had demonstrated nasal peripapillary atrophy in the left eye. The patient's cataract operation lasted for two hours, but there were no intraoperative complications. An examination one week after the operation disclosed an oval-shaped area of retinal pallor superotemporal to the fovea, oriented with the long axis in the vertical meridian. The margin of the lesion was 1 disk diameter from the fovea. Visual acuity was 20/20. A diagnosis of operating microscope burn was made.

Ocular examination at the time of the occurrence showed visual acuity of 20/25 with distortion on the Amsler grid evaluation. A chorioretinal scar corresponding to the previously noted area of retinal pallor was apparent. At the nasal edge of the scar was an area of light green subretinal discoloration approximately ¼ disk diameter in size with evidence of subretinal fluid.

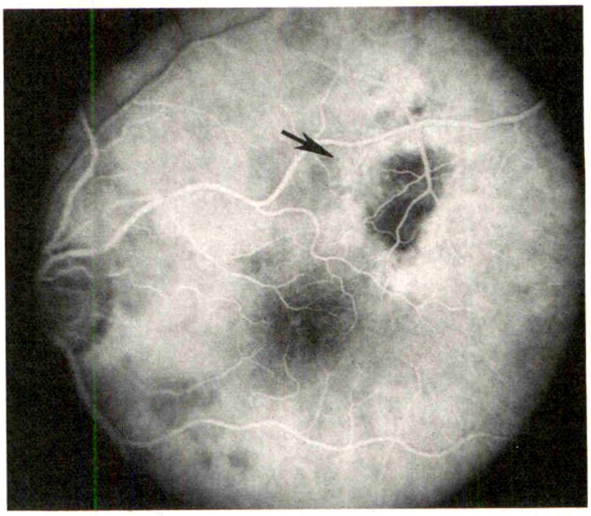


Fig. 1 (Leonardy, Dabbs, and Sternberg). Early frame of fluorescein angiogram showing the hypofluorescent oval-shaped area corresponding to the phototoxic lesion with an area of hyperfluorescence at its nasal edge (arrow).

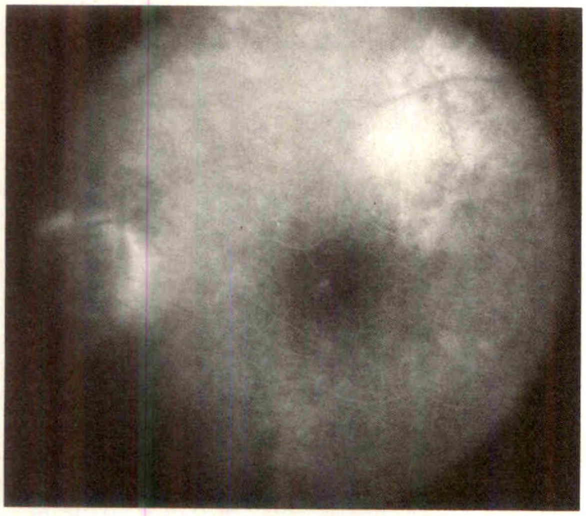


Fig. 2 (Leonardy, Dabbs, and Sternberg). The area of early hyperfluorescence leaks in this late frame of the angiogram, characteristic of subretinal neovascularization.

Fluorescein angiography showed the oval-shaped lesion was hypofluorescent with a surrounding ring of hyperfluorescence. The adjacent area became progressively hyperfluorescent during the transit phase with leakage in the late phase of the study (Figs. 1 and 2). A subretinal neovascular membrane was diagnosed and promptly treated with argon laser focal ablation. The patient's symptoms resolved. An allergic reaction to the fluorescein dye precluded posttreatment angiography. Visual acuity has improved to 20/20, and there is no ophthalmoscopic evidence of recurrence of the subretinal neovascular membrane.

Although the superotemporal location of this lesion is less common than inferior retinal lesions because of operating microscope phototoxicity, the prolonged operating time and the clinical appearance of the lesion are typical of this mechanism of retinal injury.[3] The late development of visual symptoms because of a subretinal neovascular membrane developing next to the phototoxic lesion was unique in our patient. Tso and Woodford[4] described subretinal neovascularization occurring in areas of experimentally induced phototoxicity in monkeys. These findings were discovered two to five years after exposure to 1½ to 2½ hours of light from an indirect ophthalmoscope focused on the retina.

Subretinal neovascularization has been associated with other types of chorioretinal scars, such as toxoplasmosis and trauma, presumably related to damage to the retinal pigment epithelium and Bruch's membrane.[5] Ophthalmologists should be aware of this complication, which may benefit from focal laser treatment.

References

1. McDonald, H. R., and Irvine, A. R.: Light-induced maculopathy from the operating microscope in extracapsular cataract extraction and intraocular lens implantation. Ophthalmology 90:945, 1983.
2. Lindquist, T. D., Grutzmacher, R. D., and Gofman, J. D.: Light-induced maculopathy. Potential for recovery. Arch. Ophthalmol. 104:1641, 1986.
3. Khwarg, S. G., Linstone, F. A., Daniels, S. A., Isenberg, S. J., Hanscom, T. A., Geoghegan, M., and Straatsma, B. R.: Incidence, risk factors, and morphology in operating microscope light retinopathy. Am. J. Ophthalmol. 103:255, 1987.
4. Tso, M. O. M., and Woodford, B. J.: Effect of photic injury on the retinal tissues. Ophthalmology 90:952, 1983.
5. Ryan, S. J.: Subretinal neovascularization. In Ryan, S. J. (ed.): Retina. St. Louis, C. V. Mosby, 1989, vol. II, pp. 107–125.

Chorioretinitis Induced by Coxsackievirus B4 Infection

Kyoko Hirakata, M.D.,
Takashi Oshima, M.D.,
and Noriyuki Azuma, M.D.

Department of Ophthalmology, National Children's Hospital.

Kyoko Hirakata, M.D., Department of Ophthalmology, National Children's Hospital, 3-35-31, Taishido, Setagaya-ku, Tokyo, 154, Japan.

Several viral infections may be associated with retinal complications. Such complications, however, do not occur often. Chorioretinitis has been induced by measles, rubella, varicella-zoster, herpesviruses, and cytomegalovirus.[1] We treated a patient with chorioretinitis caused by coxsackievirus B4.

An 11-year-old boy had a one-week history of high-grade fever of 38.0 to 39.5 C with general fatigue. The patient was admitted to a local hospital because of abdominal pain and vomiting. The patient was given intravenous piperacillin sodium, but no marked improvement was noted. Results of laboratory tests

showed aseptic meningitis, anemia, a high serum lactate dehydrogenase level, 1,225 mIU/ml; glutamic oxaloacetic transaminase, 87 mIU/ml; glutamic pyruvic transaminase level, 74 mIU/ml; and prolongation of the P-R interval (0.24 seconds) in the electrocardiogram. The patient was transferred to our hospital. An ophthalmic investigation was performed one week later to help in the diagnosis, although the patient had no ocular complaints.

Visual acuity was 20/20 in each eye. Slit-lamp examination showed a normal anterior segment and clear media, but ophthalmoscopy disclosed bilateral chorioretinitis. There were several scattered white lesions mainly in the midperiphery along the retinal vessels (Fig. 1). The size of the lesions ranged from 0.25 to 1.5 disk diameters. The optic disk, macula, and retinal vessels appeared normal. Intravenous latamoxef sodium was given for possible infections.

Results of laboratory tests showed a red blood cell count of $406 \times 10^6/mm^3$ and a white blood cell count of $6,700/mm^3$. Lactate dehydrogenase, glutamic oxaloacetic transaminase, and glutamic pyruvic transaminase returned to the normal levels soon after hospitalization. There were 206 cells/ml^3 in the cerebrospinal fluid (primarily lymphocytes), with a protein level of 24 mg/dl and a glucose level of 55 mg/dl. The results of computed tomographic scans of the brain, electroencephalography,

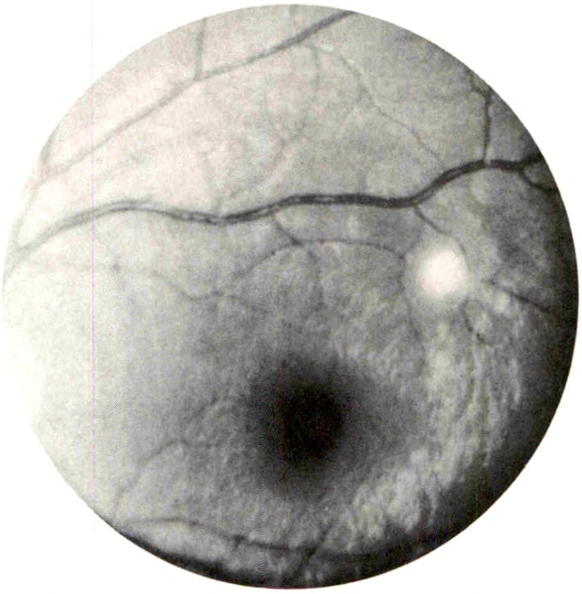


Fig. 1 (Hirakata, Oshima, and Azuma). The white chorioretinal lesion near the macula in the left eye. The lesion had some resemblance to cotton-wool patches, and the size was approximately 0.25 disk diameter.

and ultracardiography were unremarkable. Cultures of blood, cerebrospinal fluid, urine, and stool were all negative for bacteria including mycobacteria, fungi, and viruses. Serologic tests, however, disclosed serum antibody to coxsackievirus B4, at a titer of 1:64 (neutralization test). Aseptic meningitis associated with mild hepatitis and chorioretinitis induced by coxsackievirus B4 infection was diagnosed.

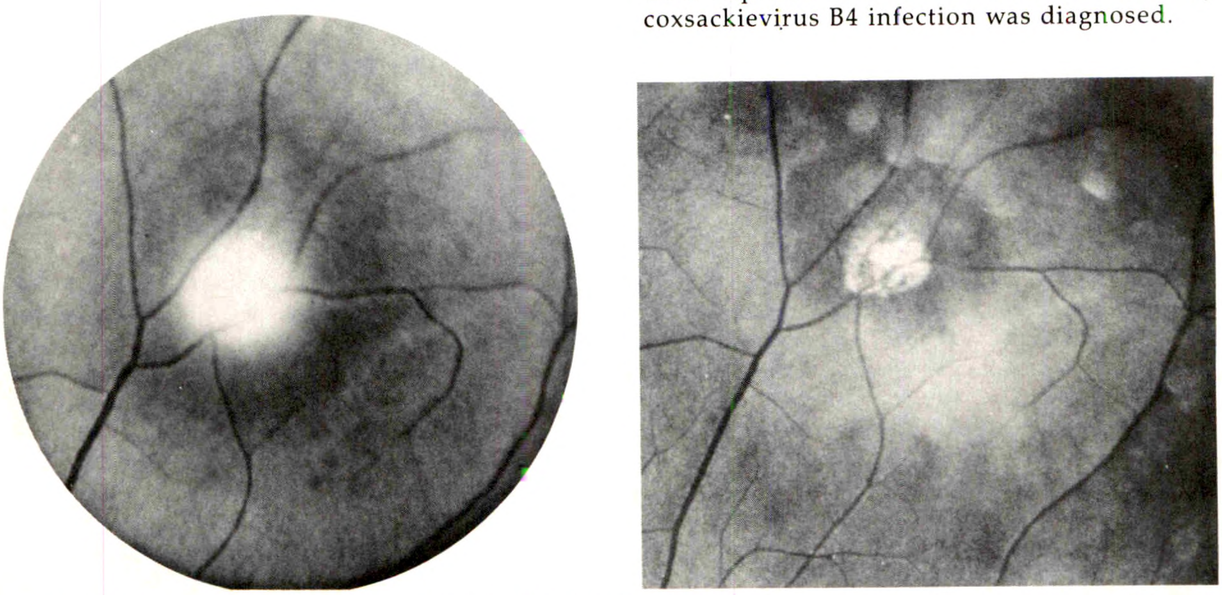


Fig. 2 (Hirakata, Oshima, and Azuma). Left, The chorioretinal lesion in the superotemporal retina of the left eye at the first visit. Right, The same lesion six months later. The lesion changed to a white scar.

Three days later fever was reduced, and the patient's general condition was improved. The cells in the cerebrospinal fluid decreased daily, and latamoxef sodium was discontinued. The P-R interval returned to normal. The neutralization test titer of the patient's serum antibody to coxsackievirus B4 decreased from 1:32 to 1:16. The neutralization test and complement fixation test were negative for other viruses.

Ophthalmoscopically, the lesions became smaller and paler, changing to white scars with pigmentation or depigmentation, with recovery, and finally disappeared except for a few scars (Fig. 2). Both visual field tests and electroretinogram performed two years later were normal.

Coxsackievirus is a kind of enterovirus which belongs to the Picornaviridae. They may cause respiratory and gastrointestinal symptoms, erythema, meningitis, meningoencephalitis, myocarditis, pericarditis, and myositis.[2] Although coxsackievirus infections are not rare, chorioretinitis is not usually identified because there is no complaint of ocular symptoms, as in our case. The chorioretinitis was self-limited and resulted in no severe visual disturbance in our case. Ophthalmoscopic examinations are recommended in cases of suspected coxsackievirus infection, especially if associated with meningitis, because it is possible that symptoms and complications may occur depending on the location of the chorioretinal lesions.

References

1. Duke-Elder, S., and Dobree, J. H.: Diseases of the Retina. In Duke-Elder, S. (ed.): System of Ophthalmology, vol. 10. London, Henry Kimpton, 1965, p. 264.

2. Behrman, R. E., and Vaughan, V. C.: Nelson Textbook of Pediatrics, ed. 13. Philadelphia, W. B. Saunders, 1987, p. 689.

Cryoprecipitated Fibrinogen (Fibrin Glue) in Orbital Surgery

George B. Bartley, M.D., and Thomas V. McCaffrey, M.D.

Departments of Ophthalmology (G.B.B.) and Otolaryngology (T.V.McC.), Mayo Clinic and Mayo Foundation.

Inquiries to George B. Bartley, M.D., Department of Ophthalmology, Mayo Clinic, 200 First St. S.W., Rochester, MN 55905.

Fibrin tissue adhesive has been used in Europe for many years in several procedures including nerve grafting, tympanoplasty, ossicular chain reconstruction, skin grafting, repair of dural tears and pulmonary leaks, and for hemostasis during cardiac, vascular, gastrointestinal, and gynecologic surgery. In ophthalmic surgery, fibrin glue has been used to secure a skin graft to an exenterated orbit,[1] to approximate the conjunctiva and to promote hemostasis during retinal detachment repair, cataract extraction, and strabismus surgery,[2] and to treat corneal perforations.[3] Fibrin glue in Europe has been prepared from homologous blood, but government restrictions in the United States prohibited the product's use until techniques for preparation from autologous blood were perfected.[4,5] Recently, fibrin glue prepared from homologous blood has been approved by the Food and Drug Administration.

We used autologous fibrin glue in the treatment of a patient with a traumatic nasal-orbital defect.

A 28-year-old man had a right orbital blow-out fracture. Surgical repair restored normal ocular motility and cosmesis. During the next two years, however, the patient had several episodes of orbital edema and low-grade cellulitis secondary to sinusitis. A dermal graft was used to occlude a fistula between the medial orbit and the nose. The patient was asymptomatic for three months before orbital inflammation recurred. Several subsequent episodes of sinusitis with orbital spillover were treated with broad-spectrum antibiotics. The patient was referred to our institution for further examination.

Visual acuity and motility of each eye were normal. The patient noted that the right orbit would feel full and the right eye would protrude when he blew his nose. Exophthalmometry confirmed 2 mm of right proptosis after this maneuver. The patient learned to reduce the globe with gentle manual pressure. Computed tomography demonstrated air within the right orbit although a fistula was not identified by nasal examination.

The right medial orbit was explored through an external ethmoidectomy incision. A defect in the periorbita was identified 34 mm posterior to the orbital margin. A fascia lata graft harvested from the iliotibial tract was used to cover the fistula and to reinforce the medial orbital boundary. The graft was secured with autologous fibrin glue (Figure). The postoperative course was uneventful with resolution of the

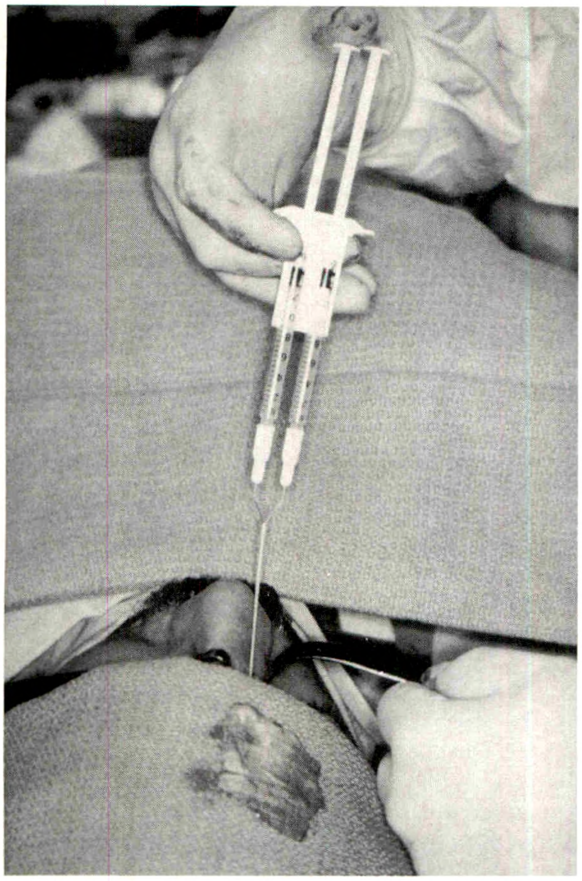


Figure (Bartley and McCaffrey). Fibrinogen and factor XIII in one barrel of double syringe mix with thrombin and calcium chloride in second barrel to form fibrin glue. Glue is used to secure fascia lata graft (on towel) to medial orbital wall.

orbital inflammation and intermittent proptosis.

Thrombin, in the presence of factor XIII, converts fibrinogen to fibrin polymer which can be used as a tissue adhesive. Coagulation factors I (fibrinogen), VIII, and XIII precipitate when fresh plasma is frozen to −70 C. After thawing and centrifugation, the concentrated fibrinogen can be isolated. Intraoperatively, fibrin glue is constituted by mixing four components delivered through a double syringe. One barrel of the syringe contains fibrinogen and factor XIII while the other contains thrombin and calcium chloride. The rate of the reaction is proportional to the concentration of thrombin. The glue promotes adhesion best when the tissues are dry. Approximately 70% of the bonding effect occurs within two minutes, with maximum strength achieved between 30 and 90 minutes.[4] The fibrin glue eventually resorbs. Aprotinin, a fibrinolysis inhibitor, is usually added to the thrombin in the European preparations but is not used at our institution. One unit of blood yields 2 to 10 ml of cryoprecipitated fibrinogen, and the product may be stored for up to one year. The laboratory techniques are straightforward and should be available through most blood banks at a modest cost.

Fibrinogen prepared from autologous and, more recently, homologous plasma is now approved for use in the United States. Fibrin glue has been used extensively in otolaryngologic, neurologic, and vascular surgery, and has several potential applications in ophthalmic surgery.

References

1. Harting, F., Koornneef, L., Peeters, H. J. F., and Gillissen, J. P. M.: Glued fixation of split-skin graft to the bony orbit following exenteration. Plast. Reconstr. Surg. 76:633, 1985.
2. Zauberman, H., and Hemo, I.: Use of fibrin glue in ocular surgery. Ophthalmic Surg. 19:132, 1988.
3. Lagoutte, F. M., Gauthier, L., and Comte, P. R. M.: A fibrin sealant for perforated and preperforated corneal ulcers. Br. J. Ophthalmol. 73:757, 1989.
4. Siedentop, K. H., Harris, D. M., and Sanchez, B.: Autologous fibrin tissue adhesive. Laryngoscope 95:1074, 1985.
5. Dresdale, A., Rose, E. A., Jeevanandam, V., Reemtsma, K., Bowman, F. O., and Malm, J. R.: Preparation of fibrin glue from single-donor fresh-frozen plasma. Surgery 97:750, 1985.

Microphthalmos With Cyst and Edwards' Syndrome

Carl Guterman, M.D.,
Emad Abboud, M.D.,
and Marilyn B. Mets, M.D.

Department of Ophthalmology and Visual Sciences, University of Chicago, and Michael Reese Hospital.

Inquiries to Marilyn B. Mets, M.D., Eye Research Laboratories, 939 E. 57th St., Chicago, IL 60637.

Microphthalmos with cyst has been associated with systemic and ocular anomalies.[1] The only genetic abnormalities associated with microphthalmos with cyst to date are 13q deletion syndrome and a ring deletion of chromosome 18.[2,3] We treated a newborn child with unilateral

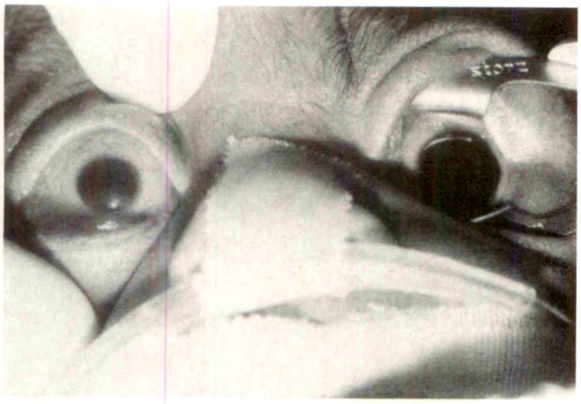


Fig. 1 (Guterman, Abboud, and Mets). The proptosed microphthalmic right eye at birth.

microphthalmos with cyst and Edwards' syndrome (trisomy 18).

A 1,600-g girl was referred on the first day of life for evaluation of unilateral proptosis. The child was born through a normal, spontaneous, vaginal delivery at 38 weeks' gestation to a 17-year-old para 3 gravida 3 mother. The two siblings were healthy children. A chromosomal disorder was suspected because the patient was small for gestational age and had low set, rotated ears, a hairy forehead, micrognathia, and rocker bottom feet.

Ocular examination showed that the right eye was proptosed, and the eyelids would not close to cover the eye (Fig. 1). The corneas measured 5.5 mm in the right eye and 8.0 mm in the left eye. A thick, persistent pupillary membrane was apparent in each eye, more prominent in the right eye. An optic nerve coloboma was apparent in the right eye. A large coloboma of the optic nerve and choroid, together with an inferior staphyloma, was apparent in the left eye. A B-scan disclosed a large cystic structure that displaced the microphthalmic right eye (Fig. 2, left). The B-scan of the left eye was normal. An orbital computed tomographic scan confirmed the ultrasound findings (Fig. 2, right). Chromosomal analysis indicated a trisomy of chromosome 18.

Trisomy 18, first described by Edwards and associates[4] in 1960, is associated with mental retardation, low birth weight, craniofacial abnormalities, congenital heart disease, horseshoe kidney, cryptorchidism, abnormalities of the hands and feet, and death in infancy. This chromosomal defect is also associated with many ocular findings including microphthalmos, uveal colobomata, and optic disk anomalies.

Microphthalmos with cyst is a structural abnormality secondary to incomplete closure of the embryonic fissure. It usually occurs unilaterally, as in our patient, with no systemic abnormalities.[1] When associated with 13q deletion or a ring deletion of chromosome 18, microphthalmos with cyst occurred bilaterally. Diagnosis of microphthalmos with cyst can be made by either B-scan or computed tomography. Because of the life expectancy of less than one year in our patient, ocular treatment was not suggested.

References

1. Foxman, S., and Cameron, J. D.: The clinical implications of bilateral microphthalmos with cyst. Am. J. Ophthalmol. 97:632, 1984.

2. Weiss, A., and Margo, C. F.: Bilateral microph-

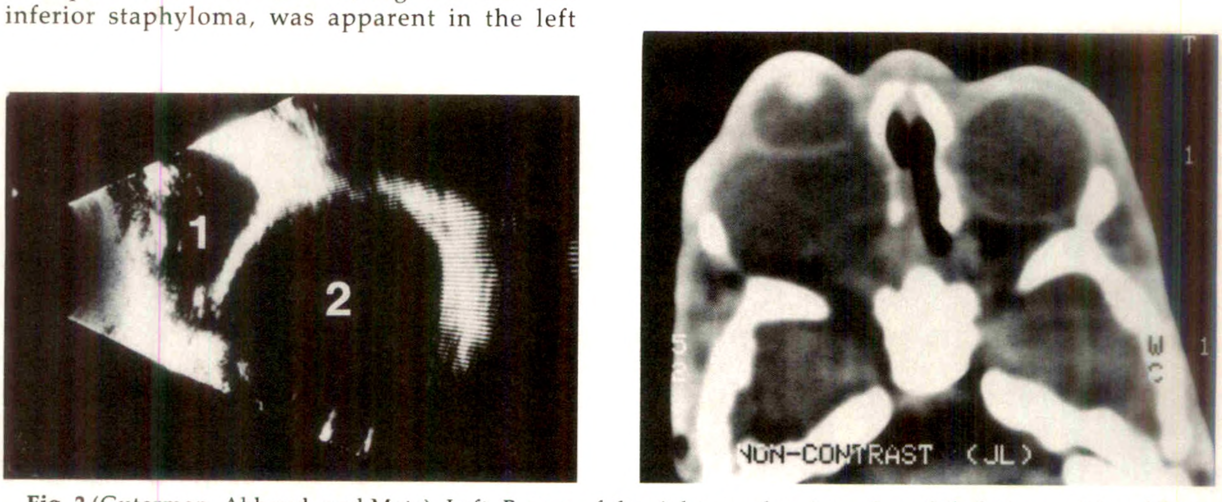


Fig. 2 (Guterman, Abboud, and Mets). Left, B-scan of the right eye showing microphthalmic eye (1) and large cystic structure adjacent to and contiguous with the globe (2). Right, Computed tomographic scan of the orbits.

thalmos with cyst and 13q deletion syndrome. Arch. Ophthalmol. 105:29, 1987.
3. Yanoff, M., Rorke, L. B., and Niederer, B. S.: Ocular and cerebral abnormalities in chromosome 18 deletion defect. Am. J. Ophthalmol. 70:391, 1970.
4. Edwards, J. H., Harnden, D. G., Cameron, A. H., Crosse, V. M., and Wolff, O. H.: A new trisomic syndrome. Lancet 1:787, 1960.

Normal Intraocular Pressure After a Bone Marrow Transplant in Glaucoma Associated With Mucopolysaccharidosis Type I-H

Stephen P. Christiansen, M.D., Thomas J. Smith, M.D., and P. Jean Henslee-Downey, M.D.

Departments of Ophthalmology (S.P.C., T.J.S.) and Hematology/Oncology (P.J.H.-D.), University of Kentucky.

Inquiries to Stephen P. Christiansen, M.D., Department of Ophthalmology, University of Kentucky, 800 Rose St., Lexington, KY 40536.

Hurler syndrome (mucopolysaccharidosis type I-H) is an inherited disorder in which a deficiency of alpha-L-iduronidase causes an accumulation of glycosaminoglycan in lysosomes. Typical systemic manifestations include coarse facial features, developmental delay, cardiopulmonary disorders, skeletal dysplasia, and hepatosplenomegaly. The ocular findings include corneal clouding, optic atrophy, and pigmentary degeneration of the retina. Glaucoma has also been reported in Hurler syndrome and has been treated by goniotomy[1] and trabeculectomy.[2] Bone marrow transplantation can ameliorate some of the systemic and ophthalmic manifestations of this disorder.[3] We treated open-angle glaucoma in a child with Hurler syndrome. Intraocular pressure returned to normal after bone marrow transplantation.

Our patient is a 3-year-old boy born at 30 weeks' gestational age by breech cesarean section. The patient's neonatal course was complicated by respiratory distress, which required mechanical ventilation. As an infant, the patient had frequent upper respiratory and ear infections. At 9 months of age, Hurler syndrome was suspected because of the patient's characteristic facies, large head size, hepatosplenomegaly, developmental delay, and cloudy corneas (Figure). The alpha-L-iduronidase level was diagnostically low. At the age of 3, the child had an ocular examination under sedation with meperidine hydrochloride, promethazine hydrochloride, and chlorpromazine. The patient had marked stromal haze and microcystic edema of each cornea. Corneal diameters were 13 mm in each eye. Intraocular pressures were R.E.: 25 mm Hg and L.E.: 38 mm Hg. The optic nerves appeared pale and had large cups. The retina appeared normal bilaterally. A second examination under sedation with ketamine hydrochloride was done. Intraocular pressures at that time were R.E.: 38 mm Hg and L.E.: 35 mm Hg. Gonioscopy with a Koeppe lens showed open angles in each eye. The patient was given 4% pilocarpine and 0.5% timolol in each eye.

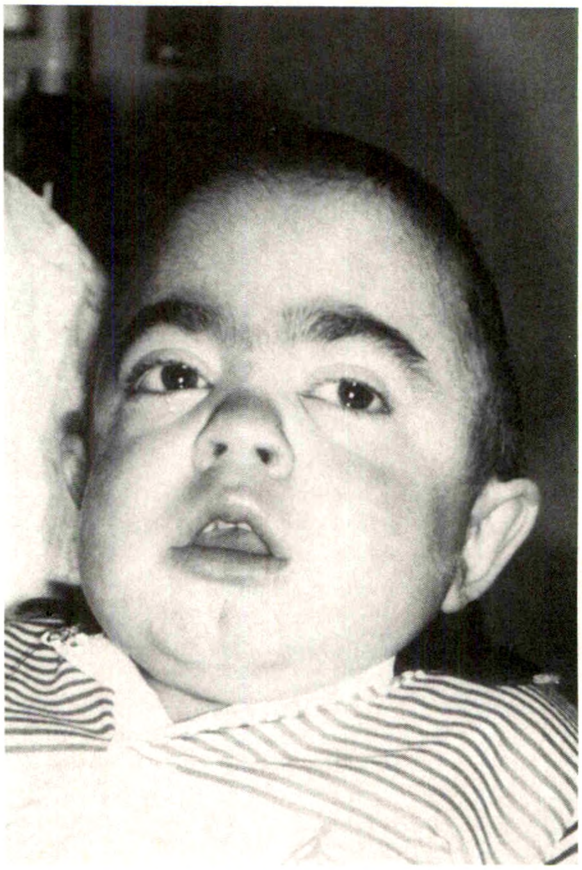


Figure (Christiansen, Smith, and Henslee-Downey). Photograph of the patient demonstrating the characteristic facial features of Hurler syndrome.

After conditioning therapy consisting of total body irradiation before high-dose chemotherapy with etoposide, cytarabine, cyclophosphamide, and methylprednisolone, the patient re-

ceived a haploidentical marrow graft from his father who had heterozygote (carrier) levels of enzyme. Engraftment was evident within two weeks. Serial measurements demonstrated enzyme activity comparable to donor levels. The posttransplant course was complicated by cutaneous graft-vs-host disease, which was successfully treated. An examination under ketamine hydrochloride sedation was performed 71 days after transplantation. Corneal diameters remained unchanged. However, there was marked clearing of the stromal haze and complete resolution of the microcystic edema. Intraocular pressures were R.E.: 14 mm Hg and L.E.: 13 mm Hg. The timolol and pilocarpine eyedrops were discontinued. Two weeks later intraocular pressures under ketamine hydrochloride sedation were R.E.: 17 mm Hg and L.E.: 16 mm Hg.

Electron microscopic evidence shows that glaucoma in children with Hurler syndrome may result from decreased aqueous outflow because of the presence of glycosaminoglycans in the outflow apparatus.[2] Bone marrow transplantation is believed to ameliorate some of the systemic manifestations of the syndrome by engraftment of functional tissue, production of the deficient enzyme, partial metabolic correction, and decreased accumulation of glycosaminoglycan.[4] The intraocular pressures returning to normal, demonstrated by our case, suggests that there may be a reduction of glycosaminoglycan in the outflow apparatus after bone marrow transplantation. It may be prudent, in those patients with Hurler syndrome and glaucoma who are candidates for bone marrow transplantation, to await the outcome of bone marrow transplantation before proceeding with surgical therapy for the glaucoma.

References

1. Nowaczyk, M. J., Clarke, J. T. R., and Morin, J. D.: Glaucoma as an early complication of Hurler's disease. Arch. Dis. Child. 63:1091, 1988.
2. Spellacy, E., Bankes, J. L. K., Crow, J., Dourmashkin, R., Shah, D., and Watts, R. W. E.: Glaucoma in a case of Hurler disease. Br. J. Ophthalmol. 64:773, 1980.
3. Summers, C. G., Purple, R. L., Krivit, W., Pineda, R., Copland, G. T., Ramsay, N. K. C., Kersey, J. H., and Whitley, C. B.: Ocular changes in the mucopolysaccharidoses after bone marrow transplantation. Ophthalmology 96:977, 1989.
4. Whitley, C. B., Ramsay, N. C. K., Kersey, J. H., and Krivit, W.: Bone marrow transplantation for Hurler syndrome. Assessment of metabolic correction. Birth Defects 22:7, 1986.

Necrotizing Scleritis Secondary to Conjunctival Squamous Cell Carcinoma in Acquired Immunodeficiency Syndrome

Robert Y. Kim, M.D.,
Stuart R. Seiff, M.D.,
Edward L. Howes, Jr., M.D.,
and James J. O'Donnell, M.D.

Departments of Ophthalmology (R.Y.K., S.R.S., E.L.H., J.J.O.) and Pathology (E.L.H.), University of California.

Inquiries to Stuart R. Seiff, M.D., Department of Ophthalmology, Room K301, University of California, San Francisco, CA 94143.

Necrotizing scleritis is a rare manifestation of squamous cell carcinoma of the conjunctiva. We encountered a case that occurred in a man with acquired immunodeficiency syndrome.

A 61-year-old homosexual man with AIDS noted redness and irritation in the left eye. Visual acuity was 20/20 in each eye. The right eye had a pterygium. On the left eye was a pink, elevated, vascularized conjunctival mass 4 mm lateral to the corneoscleral limbus with mild thinning of the sclera between the corneoscleral limbus and the mass. The anterior chamber was deep and quiet. Gonioscopy showed no invasion of the angle. Both fundi were normal. Over the next two weeks, the sclera became progressively thinner, resulting in a 3 × 5-mm area of bulging uvea covered by an extremely thin layer of sclera (Fig. 1). An excisional biopsy specimen of the enlarging conjunctival mass adjacent to the staphyloma disclosed squamous cell carcinoma with invasion of the superficial sclera and left lateral rectus muscle (Fig. 2).

Because of the patient's poor health, limited life expectancy, and risk of loss of vision in the fellow eye from viral retinitis, palliative debulking of the conjunctival tumor with cryotherapy to the underlying sclera was performed. A preserved sclera graft was sutured over the bulging uvea. Oral mucous membrane was grafted over the area of resected conjunctiva.

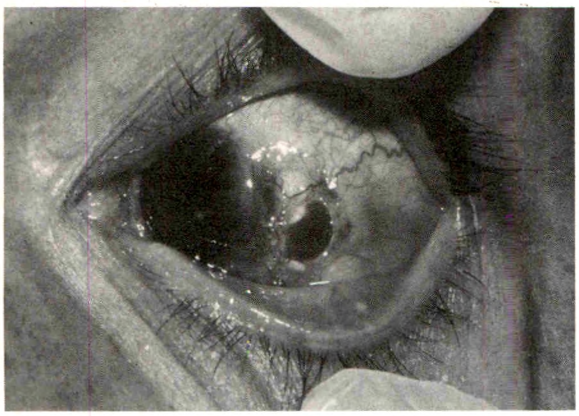


Fig. 1 (Kim and associates). Left eye. Conjunctival mass with adjacent scleral thinning.

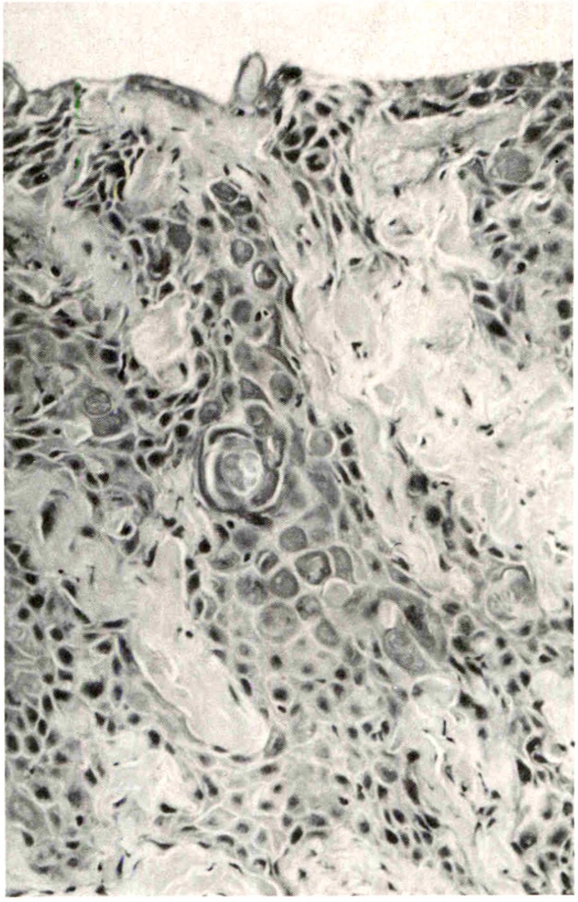


Fig. 2 (Kim and associates). Squamous cell carcinoma of the conjunctiva invading into the submucosa (hematoxylin and eosin, × 200).

One week postoperatively, visual acuity was L.E.: 20/50. Abduction of the left eye was moderately diminished. Both grafts were healing well. Three and one-half weeks postoperatively, the patient suffered the third episode of *Pneumocystis carinii* pneumonia and died of respiratory arrest. The left eye was unavailable for postmortem examination.

Two cases reported in the literature describe necrotizing scleritis associated with scleral perforation and intraocular invasion by the tumor.[1,2] Stokes[1] described a 72-year-old man who developed scleritis with scleral perforation in a region from which a squamous cell carcinoma of the conjunctiva had been removed several months earlier. Examination of the globe showed intraocular invasion by the tumor. Lindenmuth and associates[2] described a 64-year-old man who had necrotizing scleritis, scleral perforation, and uveal prolapse as the initial manifestation of invasive squamous cell carcinoma of the conjunctiva.

Squamous cell carcinomas of the lung, oral cavity, epiglottis, esophagus, anorectum, and skin have been reported in patients with AIDS, AIDS-related complex, and human immunodeficiency virus seropositivity.[3,4] Winward and Curtin[5] recently reported a case of conjunctival squamous cell carcinoma in a man who was HIV seropositive. Although firm epidemiologic data are lacking, the number of anecdotal reports suggests an increased incidence of aggressive squamous cell carcinomas in patients with HIV-related disease. Our case is an uncommonly aggressive manifestation of this type of tumor and may be related to the patient's underlying AIDS. Physicians confronted with such tumors might consider HIV testing if the status is not already known.

References

1. Stokes, J. J.: Intraocular extension of epibulbar squamous cell carcinoma of the limbus. Trans. Am. Acad. Ophthalmol. Otolaryngol. 59:143, 1955.
2. Lindenmuth, K. A., Sugar, A., Kincaid, K. C., Nelson, C. C., and Comstock, C. P.: Invasive squamous cell carcinoma of the conjunctiva presenting as necrotizing scleritis with scleral perforation and uveal prolapse. Surv. Ophthalmol. 33:50, 1988.
3. Overly, W. L., and Jakubek, D. J.: Multiple squamous cell carcinomas and human immunodeficiency virus infection. Ann. Intern. Med. 106:334, 1987.
4. Frager, D. H., Wolf, E. L., Comptetiello, L. S., Frager, J. D., Klein, R. S., and Beneventano, T. C.: Squamous cell carcinoma of the esophagus in pa-

tients with acquired immunodeficiency syndrome. Gastrointest. Radiol. 13:358, 1988.

5. Winward, K. E., and Curtin, V. T.: Conjunctival squamous cell carcinoma in a patient with human immunodeficiency virus infection. Am. J. Ophthalmol. 107:554, 1989.

Bilateral Paralimbal Scleromalacia Perforans

Thomas H. Mader, M.D., R. Doyle Stulting, M.D., and Hal H. Crosswell, Jr., M.D.

The Emory Eye Center, Emory University School of Medicine (T.H.M., R.D.S.), and Department of Ophthalmology, University of South Carolina School of Medicine (H.H.C.).

Inquiries to Thomas H. Mader, M.D., Cornea Service, Emory Eye Center, 1327 Clifton Rd. N.E., Atlanta, GA 30322.

Paralimbal scleromalacia perforans is a rare condition characterized by a slowly progressive, noninflammatory, painless scleral thinning at the corneoscleral limbus, which leads to iris prolapse.[1] It occurs in young adults in the absence of systemic disease or previous ocular inflammation.[1,2] This condition is in sharp contrast to most cases of scleral thinning that are usually seen in association with local ocular inflammation or concurrent chronic systemic inflammatory disease. Paralimbal scleromalacia perforans is reported to have a good prognosis without treatment.[2]

In October 1983 a 33-year-old woman had a one-year history of foreign body sensation and a ten-day history of decreased vision in the right eye. The patient had no history of ocular pain, inflammation, or previous ocular problems. Medical history and family history did not indicate rheumatoid disease or any other significant systemic disease. Visual acuity was R.E.: 20/40 and L.E.: 20/20. Both pupils reacted normally to light, but the right pupil was slightly displaced superonasally. Intraocular pressures by applanation tonometry were R.E.: 1 mm Hg and L.E.: 9 mm Hg. The patient had bilateral paralimbal scleral thinning from the 10 o'clock to the 3 o'clock meridian in the right eye and from the 8 o'clock to 2 o'clock meridian in the left eye with almost complete absence of the sclera on the right eye. The iris could be seen through the conjunctiva and sclera. There were no signs of inflammation. A diffuse subconjunctival bleb was superior to the thin sclera. The anterior chambers were clear and of normal depth. Using gonioscopy, a slit opening was visible in the right eye along the trabecular meshwork from the 12 o'clock to 2 o'clock meridian. The corneas and lenses were clear. Mild disk edema was present in the right eye.

Results of laboratory studies including complete blood cell count, platelet count, VDRL test, erythrocyte sedimentation rate, urinalysis, electrolyte count, antinuclear antibody level, vitamin A level, rheumatoid factor, and serum protein electrophoresis were normal. No ocular therapy was instituted after initial examination. Spectacles were recommended during the day and a shield at night to protect against inadvertent trauma. An examination in January 1984 disclosed further thinning of the sclera superiorly in the right eye. Over the next three months, the sclera continued to thin at the corneoscleral limbus bilaterally, more progressive in the right eye. In March 1984, with intraocular pressure of 0 mm Hg in the right eye and decreasing visual acuity, visual fields confirmed enlargement of the blind spot. A lamellar sclerokeratoplasty was performed to reinforce the area of extreme scleral thinning. Two months after the operation, a subconjunctival filtering bleb was noted at the superior border of the lamellar graft. By six months postoperatively, the patient's visual acuity was correctable to 20/25 in the right eye. The vision remained stable for the next three years. In early 1988 the patient returned with a corrected

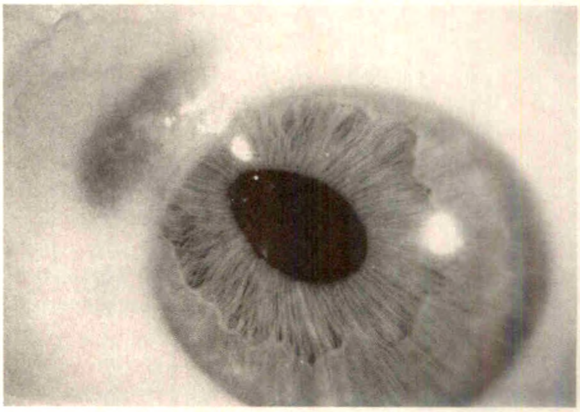


Fig. 1 (Mader, Stulting, and Crosswell). Scleromalacia with peaked pupil in the left eye.

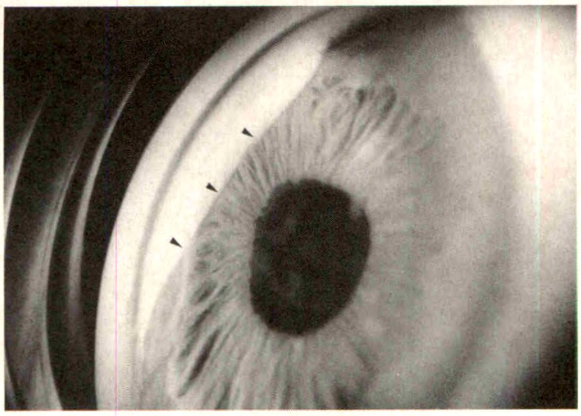


Fig. 2 (Mader, Stulting, and Crosswell). Gonioscopy of the left eye showing iris incarceration into linear scleral perforation.

visual acuity of 20/20 in both eyes. The intraocular pressure was R.E.: 6 mm Hg and L.E.: 8 mm Hg. The left pupil was peaked toward the 10 o'clock meridian. Gonioscopy showed iris incarceration into a linear scleral perforation along the trabecular meshwork from the 10 o'clock to 12 o'clock meridian (Figs. 1 and 2). Repeated physical examinations over a five-year period disclosed no systemic illness.

This is a case of bilateral indolent loss of tissue at the corneoscleral junction in an otherwise healthy woman. This condition, known as paralimbal scleromalacia perforans or spontaneous scleral intercalary perforation, was first described as a clinical entity by Franceschetti and Bischler in 1950.[3] Using the strict criterion of painless, noninflammatory, spontaneous paralimbal thinning in the absence of systemic disease or ocular inflammation, two cases have been reported.[4] This condition appears to be a degenerative process that occurs at the corneoscleral junction in the area of the trabecular meshwork. One report suggests that a small vessel may run through the defect to anastomose with the posterior ciliary circulation. This may be the site of spontaneous perforation.[5] We saw no evidence of anastomosing vessels in our patient. We believe the disease involves a progressive scleral thinning at the trabecular meshwork. Thinning may progress to a linear perforation with incarceration of uveal tissue. This condition is described as entirely benign, nonprogressive, and requiring no treatment.[5] However, our case demonstrates that paralimbal scleromalacia perforans can cause visual loss from chronic hypotony.

References

1. François, J.: Scleromalacia perforans, arthritis deformans and pemphigus. Trans. Ophthalmol. Soc. U.K. 71:61, 1951.
2. Duke-Elder, S., and Leigh, A. G.: Diseases of the Outer Eye. Cornea and Sclera. In Duke-Elder, S. (ed.): System of Ophthalmology, vol. 8, pt. 2. St. Louis, C. V. Mosby, 1965, pp. 1054–1055.
3. Franceschetti, A., and Bischler, V.: La sclerite nodulaire nicrosante et ses rapports avec la scleromalacia. Ann. Ocul. 183:737, 1950.
4. Sorensen, T. B.: Paralimbal scleromalacia. Acta Ophthalmol. 53:901, 1975.
5. Watson, P.: Diseases of the sclera and episclera. In Duane, T. D. (ed.): Clinical Ophthalmology, vol. 4. Hagerstown, Harper & Row, 1979, p. 36.

Horizontal Homonymous Sectoral Field Defect After Ischemic Infarction of the Occipital Cortex

Murray Grossman, M.D., Steven L. Galetta, M.D., Charles W. Nichols, M.D., and Robert I. Grossman, M.D.

Department of Neurology (M.G., S.L.G.) and Radiology (R.I.G.), Hospital of the University of Pennsylvania, and Department of Ophthalmology, Scheie Eye Institute (S.L.G., C.W.N.).

Inquiries to Murray Grossman, M.D., Department of Neurology, Hospital of the University of Pennsylvania, 3400 Spruce St., Philadelphia, PA 19104.

In cases of horizontal sectoral visual field defects, lesions have been restricted to the lateral geniculate nucleus of the thalamus[1,2] or the optic radiations.[3,4] We treated a patient with a horizontal homonymous sectoral field defect after an ischemic infarct to the occipital cortex in the region of the calcarine fissure.

A 77-year-old right-handed man was noted during routine examination to have a homonymous defect in the left visual field. The patient was observed in the clinic for borderline increased intraocular pressure that had been stable for 2½ years. A slight optic cup asymmetry was present (right eye, 0.3; left eye, 0.2). Results of computerized perimetry were normal several months before this occurrence. Medical history was significant for systemic hyperten-

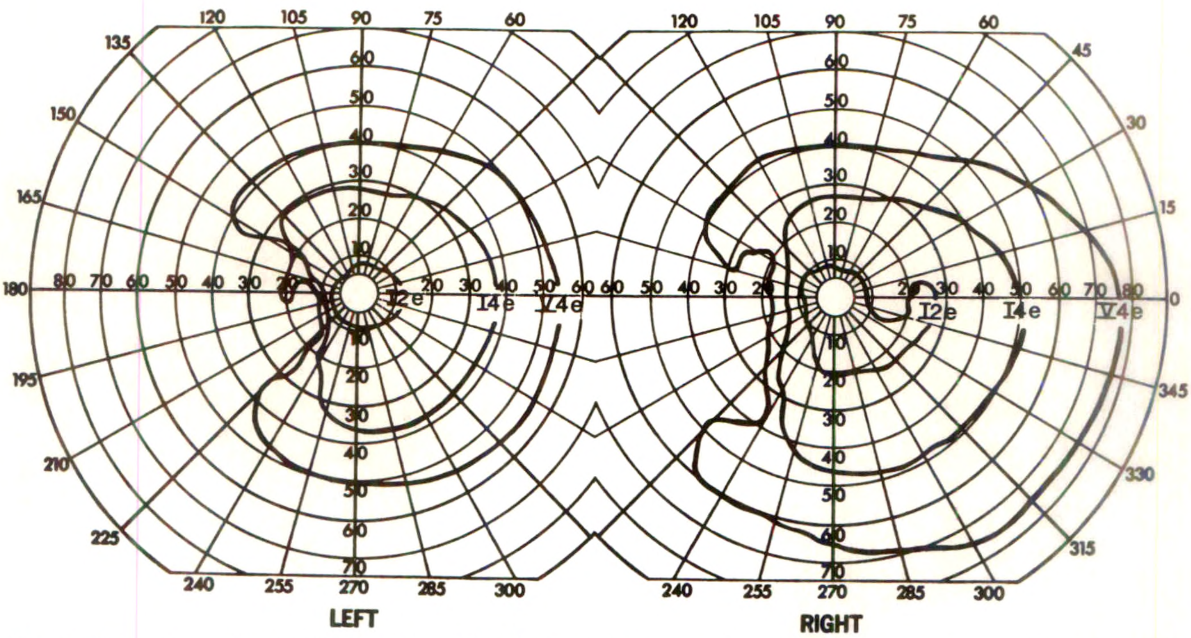


Fig. 1 (Grossman and associates). Visual fields illustrating a wedge-shaped homonymous defect extending along the horizontal meridian.

sion and rheumatic fever. Physical examination disclosed a blood pressure of 140/90 mm Hg and an irregularly irregular pulse averaging 90 beats per minute. Best-corrected visual acuity was 20/20 in each eye. Pupil diameters were 3 mm bilaterally and briskly reactive to light. Goldmann and confrontation visual fields showed a homonymous horizontal sectoral defect in the left visual field (Fig. 1), which was confirmed by computerized perimetry. Ophthalmoscopy showed arteriovenous nicking without sectoral optic atrophy. Laboratory tests disclosed a positive test for microhemagglutination of *Treponema pallidum*. Cerebrospinal fluid showed no cells, a glucose level of 75 mg/dl, a protein level of 38 mg/dl, and a nonreactive VDRL reagent. An electrocardiogram disclosed atrial fibrillation. Magnetic resonance imaging of the brain showed high signal intensity along the calcarine fissure of the right occipital lobe (Fig. 2).

Horizontal homonymous sectoral field defects are most frequently associated with ischemic insult to the lateral geniculate nucleus of the thalamus.[1,2] Interruption of the posterior lateral choroidal artery, which perfuses the central portion of the lateral geniculate nucleus, impairs vision in a corresponding horizontal wedge of both visual fields.[5] The undisturbed perfusion of the anterior hilus and anterior and lateral aspects of the lateral geniculate nucleus by the anterior choroidal artery is thought to allow preserved vision in superior and inferior portions of the same hemifield.

A horizontal homonymous sectoral field defect is not diagnostic of ischemia in the lateral geniculate nucleus of the thalamus. Several recent reports describe similar horizontal sectoral field defects after insult to the optic radiations.[3,4] In these cases, computed tomographic images show that the insult typically destroys a narrow band of white matter but spares fibers of the optic radiations coursing superiorly and inferiorly to the lesion.

Our case broadens the anatomic substrate for this unusual visual field defect. Our patient had many risk factors for a vascular insult. Regardless of the specific cause, T_2-weighted magnetic resonance images in axial and coronal planes, and confirmed by a sagittal image, indicate that the patient probably suffered a selected occlusion of a penetrating branch of the right calcarine artery in the area of the calcarine fissure.[5] The magnetic resonance images also show some mild periventricular high signal intensity, a common finding in patients older than 55 years.

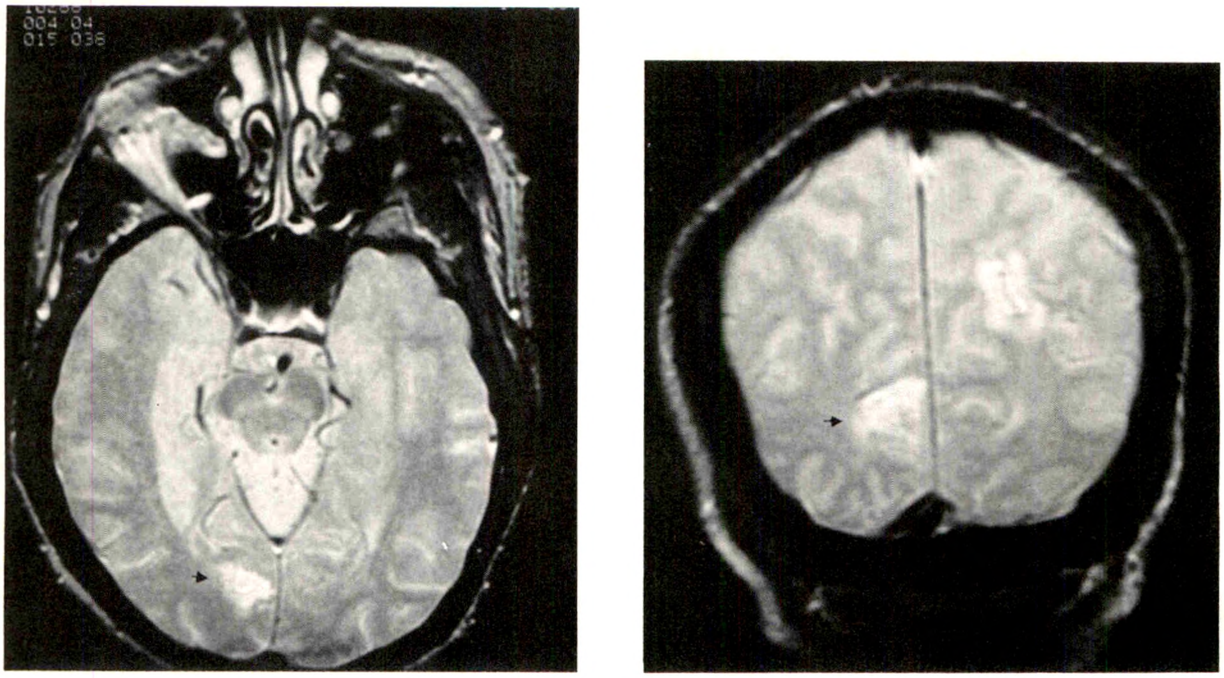


Fig. 2 (Grossman and associates). High signal intensity in the right occipital lobe in the region of the calcarine fissure, indicated by the arrows, demonstrated by axial (left) and coronal (right) magnetic resonance imaging utilizing parameters of repetition time = 3,000 msec, echo time = 90 msec, number of excitations = 1.

It is unlikely that this accounts for the patient's visual field defect, because an identical finding in the contralateral hemisphere did not result in a right-sided visual field defect. The magnetic resonance images also showed the lateral geniculate nucleus to be structurally intact. Our case demonstrates that horizontal homonymous sectoral field defects are not diagnostic of ischemia in the lateral geniculate nucleus, but may occur with any strategically placed lesion posterior to lateral geniculate nucleus, including both optic radiations and occipital cortex.

References

1. Frisen, L.: Quadruple sectoranopia and sectoral optic atrophy. A syndrome of the distal anterior choroidal artery. J. Neurol. Neurosurg. Psychiatry 42:590, 1979.

2. Shacklett, D. E., O'Connor, P. S., Dorwart, R. H., Linn, D., and Carter, J. E.: Congruous and incongruous sectoral visual field defects with lesions of the lateral geniculate nucleus. Am. J. Ophthalmol. 98:283, 1984.

3. Carter, J. E., O'Connor, P., Shacklett, D., and Rosenberg, M.: Lesions of the optic radiations mimicking lateral geniculate nucleus visual field defects. J. Neurol. Neurosurg. Psychiatry 48:982, 1985.

4. Smith, R. J. S.: Horizontal sectoral hemianopia of non-traumatic origin. Br. J. Ophthalmol. 54:208, 1970.

5. Lindenberg, R., Walsh, F. D., and Sacks, J. G.: Neuropathology of Vision. Philadelphia, Lea & Febiger, 1973, pp. 440–488.

Tonic Pupils as a Result of Botulism

Deborah I. Friedman, M.D.,
Vincent N. Fortanasce, M.D.,
and Alfredo A. Sadun, M.D.

Department of Ophthalmology, Doheny Eye Institute, University of Southern California.

Inquiries to Alfredo A. Sadun, M.D., Department of Ophthalmology, Doheny Eye Institute, University of Southern California, 1355 San Pablo St., Los Angeles, CA 90033.

A 25-year-old woman developed intestinal obstruction and underwent laparotomy and resection of the necrotic small bowel in January 1988. Abdominal adhesions from a previous

appendectomy were found. On the fifth postoperative day, she had weakness and respiratory difficulty, which required intubation and mechanical ventilation. A neurologic consultant found total ophthalmoplegia and proximal muscle weakness. The diagnosis of botulism was considered as most likely, and she was given polyvalent botulism antitoxin. The pretreatment serum specimen was positive for type A botulism by mouse bioassay. The posttreatment serum was negative for toxin. The patient recovered sufficiently after two months and was discharged from the hospital.

Persistent pupillary dilation and poor vision at near prompted neuro-ophthalmologic referral in April 1988. The patient did not complain of diplopia. Examination showed less than 1 diopter of accommodative range in both eyes. The pupil diameter was 7 mm bilaterally with no constriction to light, and a trace tonic near response. Slit-lamp examination disclosed iris sector palsies in both eyes. Ocular motility was normal. Instillation of 0.1% pilocarpine (1 drop in both eyes, repeated after ten minutes) produced pupillary constriction to 3 mm in 30 minutes. Follow-up examination three months later showed 8-mm pupil diameter with light-near dissociation, segmental palsies, and impaired accommodation.

Botulinum toxin blocks cholinergic transmission in the peripheral nervous system. All ganglionic synapses, postganglionic parasympathetic synapses, and neuromuscular junctions are affected. The toxin alters the ability of intracellular calcium to trigger exocytosis of acetylcholine at these sites.[1] Eight distinct immunologic types of botulinum toxin have been identified. Types A, B, and E infect humans, with type A being the most potent.

Neuro-ophthalmic complications of botulism include bilateral blepharoptosis, progressive ophthalmoplegia, blurred vision, and dilated, poorly reactive pupils. These ocular manifestations have been reported with infection by all types of human botulism organisms.[2]

The site of the lesion in idiopathic Adie's tonic pupils is believed to be at the ciliary ganglion.[3] Acute denervation produces a large pupil that is fixed to light and usually to near. Within days, hypersensitivity of the sphincter muscles, a miotic reaction to weak cholinomimetic drugs, and sectoral iris contractions are visible with slit-lamp examination. The pupil size gradually decreases, but light-near dissociation persists as the reinnervation to the ciliary muscle and pupillary sphincter is supplied by the more numerous accommodation fibers.[4]

Tonic pupils in botulism could be produced by action of the toxin at the ciliary ganglion, the neuromuscular junction to the ciliary muscles and pupillary sphincter, or a combination thereof. Studies of botulinum toxin in rat skeletal muscle have demonstrated resprouting of nerve terminals within the first week.[5] This suggests that a typical time course of pupillary recovery, similar to Adie's pupils, could be seen after botulism toxicity at either the neuromuscular junction or the ciliary ganglion.

Tonic pupils may be seen in the Holmes-Adie syndrome of tonic pupils, areflexia, autonomic neuropathies, Miller-Fisher syndrome, a variety of inflammatory and infectious diseases (herpes zoster, chicken pox, measles, diphtheria, syphilis, sarcoidosis, scarlet fever, pertussis, smallpox, influenza, sinusitis, Vogt-Koyanagi-Harada syndrome, rheumatoid arthritis, acute epidemic nephropathy), trauma, and quinine toxicity.[3] Botulism should be included among the toxic causes of this entity.

References

1. Simpson, L. L.: Molecular pharmacology of botulinum toxin and tetanus toxin. Ann. Rev. Pharmacol. Toxicol. 26:427, 1986.
2. Cherington, M.: Botulism. Ten year experience. Arch. Neurol. 30:432, 1974.
3. Miller, N. R.: Walsh and Hoyt's Clinical Neuro-Ophthalmology. Baltimore, Williams & Wilkins, 1985, pp. 492–500.
4. Loewenfeld, I. E., and Thompson, S. H.: Mechanism of tonic pupil. Ann. Neurol. 10:275, 1981.
5. Duchen, L. W.: Changes in motor innervation by botulism toxin in skeletal muscle of the mouse. Differences between fast and slow fibers. J. Neurol. Neurosurg. Psychiatry 33:40, 1970.

Intermittent Pupillary Dilatation Associated With Astrocytoma

John P. Berreen, B.S.,
Michael P. Vrabec, M.D.,
and Paul L. Penar, M.D.

Department of Surgery, Division of Ophthalmology (J.P.B., M.P.V.) and Division of Neurosurgery (P.L.P.), University of Vermont College of Medicine.

Inquiries to Michael P. Vrabec, M.D., 1 S. Prospect St., Burlington, VT 05401.

Intermittent unilateral mydriasis is extremely uncommon as the sole symptom of an intracerebral neoplasm. The time course of the fluctuations in pupillary diameter can be invaluable in defining an origin. We treated a patient in whom this isolated phenomenon indicated the presence of a frontal lobe astrocytoma.

A 33-year-old woman was seen by her primary care physician because of the recent onset of fluctuation of the pupil diameter in her left eye. The patient described a sensation of "waves of crawling" in this eye that had occurred intermittently for the previous seven days, frequently lasting one minute. She also noted her left pupil to dilate widely and then constrict with a similar periodicity. These fluctuations were confirmed by a nurse on one occasion. A sensation of mild retro-orbital pressure was apparent for approximately one week before the pupillary changes. The patient denied any other complaints or associated symptoms, including headache, blepharoptosis, diplopia, vertigo, photophobia, decreased visual acuity, focal or generalized decrease in sensation or muscle strength, or incontinence. The patient had no history of seizures, migraine headache, high blood pressure, cerebral vascular abnormalities, or ocular disease. She was taking no medications at the time of the consultation. Results of ophthalmic and neurologic examinations for pupillary function, color vision, exophthalmometry, optokinetic nystagmus, and Goldmann perimetry were normal.

Magnetic resonance imaging showed a potential mass lesion in the left frontal lobe predominantly in the white matter (Figure). No extension to the optic nerve or tract was visible. The patient underwent a left frontal craniotomy with complete removal of the mass and had no postoperative deficits. The patient recovered with no signs of recurrence or abnormal pupil function. Histologic evaluation confirmed a low-grade astrocytoma with good margins of resection.

Unilateral pupillary dilatation may result from either excitation or irritation of sympathetic fibers or inhibition or destruction of parasympathetic fibers.[1,4,5] Most documented cases of unilateral mydriasis are characterized by cycle times significantly slower than that noted in our patient. Ophthalmoplegic migraine has been reported by Woods, O'Connor, and Fleming[1] with internal ophthalmoplegia as an isolated symptom, but the duration of mydriasis was between 15 minutes and 24 hours. The time course of the mydriasis noted during seizures has been approximately 30 minutes.[2] Additionally, the time scale of the fluctuations of pupillary diameter resulting from intracerebral aneurysm and pharmacologic manipulation is characteristically much greater than that noted in our patient.

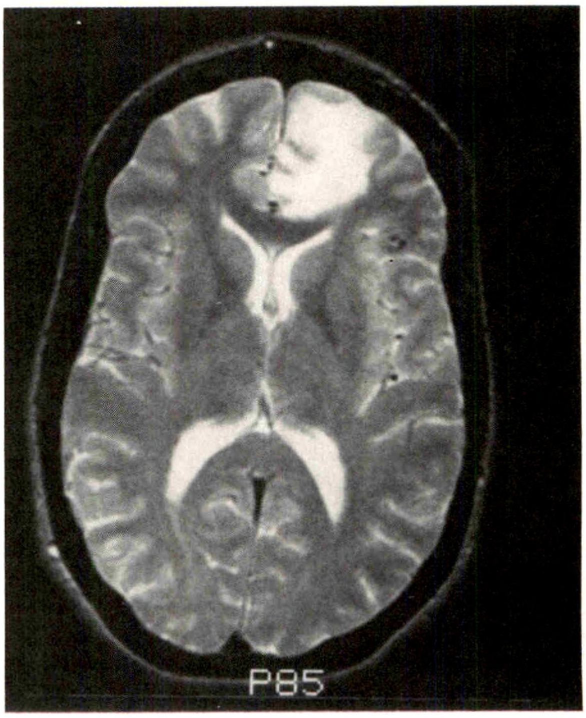


Figure (Berreen, Vrabec, and Penar). Magnetic resonance scan showing a large region of intraparenchymal high signal in the white matter of the left frontal lobe (T_2-weighted image).

Jampel[3] described a sympathetic relay in the macaque brain that originates in the frontal cortex and causes unilateral mydriasis when stimulated. This pathway, as well as parasympathetic inhibitory relays,[4] may also exist in humans and could be directly affected by a local neoplasm. A low-grade astrocytoma, not known for its intrinsic destructive ability, may be more likely to cause irritation of these fibers than destruction. The location of the mass in our patient is consistent with the interruption of the normal functioning of either of these pathways.

Because our case is unusual for an intracerebral neoplasm, it is difficult to argue in favor of a complete neurologic evaluation with magnetic resonance imaging in the absence of any other signs or symptoms. It may, however,

indicate the need for closer scrutiny and follow-up of patients with these symptoms, including radiologic studies if cerebral abnormalities are suspected.

References

1. Woods, D., O'Connor, P. S., and Fleming, R.: Episodic unilateral mydriasis and migraine. Am. J. Ophthalmol. 98:229, 1984.
2. Pant, S., Benton, J., and Dodge, P.: Unilateral pupillary dilatation during and immediately following seizures. Neurology 16:837, 1960.
3. Jampel, R.: Convergence, divergence, pupillary reactions and accommodation of the eyes from faradic stimulation of the macaque brain. J. Comp. Neurol. 115:371, 1960.
4. Ward, A., and Reed, H.: Mechanism of pupillary dilatation elicited by cortical stimulation. J. Neurophysiol. 9:329, 1946.
5. Cole, M., and Berghuis, J.: The reverse Horner syndrome. J. Thorac. Cardiovasc. Surg. 59:603, 1970.

Cyclosporine-Induced Trichomegaly

Daniel T. Weaver, M.D.,
and George B. Bartley, M.D.

Department of Ophthalmology, Mayo Clinic.

Inquiries to George B. Bartley, M.D., Department of Ophthalmology, Mayo Clinic, 200 First St. S.W., Rochester, MN 55905.

Cyclosporine has recently been included in the differential diagnosis of acquired hypertrichosis.[1] Systemic causes include porphyria, anorexia nervosa, malnutrition, dermatomyositis, hypothyroidism, and pregnancy. Drug-induced generalized hypertrichosis has been associated with diazoxide, phenytoin, minoxidil, streptomycin, corticosteroids, penicillamine, and psoralens.[1]

We examined four patients in whom acquired trichomegaly (eyelash hypertrichosis) has occurred during systemic cyclosporine therapy. Two patients had received renal allografts, one had received a hepatic allograft, and one had systemic lupus erythematosus with severe refractory thrombocytopenia. Each patient noted generalized hypertrichosis soon after the onset of cyclosporine therapy and excessive eyelash growth after three to four months of treatment. All four patients were receiving decreasing corticosteroid doses at the onset of hypertrichosis and trichomegaly.

Trichomegaly may represent an ophthalmic manifestation of generalized hypertrichosis secondary to systemic cyclosporine therapy. The factors regulating the growth cycle of the hair follicle remain obscure. Recent evidence suggests that cyclosporine induces resting (telogen) follicles to enter an active (anagen) growth phase.[2] While not a significant clinical problem, trichomegaly may reflect an underlying disorder in the patient's cellular immunity. A recent report documented trichomegaly in acquired immunodeficiency syndrome in the absence of other known precipitants of generalized hypertrichosis.[3] The finding of trichomegaly in a patient without a known precipitating systemic or pharmacologic cause should prompt the clinical suspicion of immune system abnormality.

References

1. Fenton, D. A.: Hypertrichosis. Semin. Dermatol. 4:58, 1985.
2. Paus, R., Stenn, K. S., and Link, R. E.: The induction of anagen hair growth in telogen mouse skin by cyclosporin A administration. Lab. Invest. 60:365, 1989.
3. Casanova, J. M., Puig, T., and Rubio, M.: Hypertrichosis of the eyelashes in acquired immunodeficiency syndrome (letter to the editor). Arch. Dermatol. 123:1599, 1987.

Electron Microscopic Evidence of Acarine Infestation of the Eyelid Margin

Frank P. English, F.R.C.S.,
Guang Wen Zhang, M.D.,
Don P. McManus, B.Sc.,
and Phillip Campbell, A.D.C.L.T.

Departments of Ophthalmology, St. Andrews Hospital (F.P.E.) and Queensland Institute of Medical Research (G.W.Z., D.P.McM.), and Department of Electron Microscopy, Queensland University of Technology (P.C.).

Inquiries to Frank P. English, F.R.C.S., 113 Wickham Terrace, Brisbane 4000, Australia.

Studies by Italian researchers have demonstrated demodectic mites on facial skin with

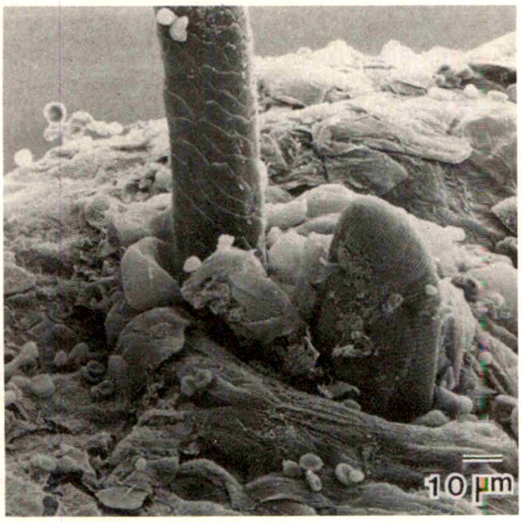


Fig. 1 (English and associates). Scanning electron microscopic view of eyelid margin displaying the protruding tail of a demodectic mite beside an eyelash (× 550).

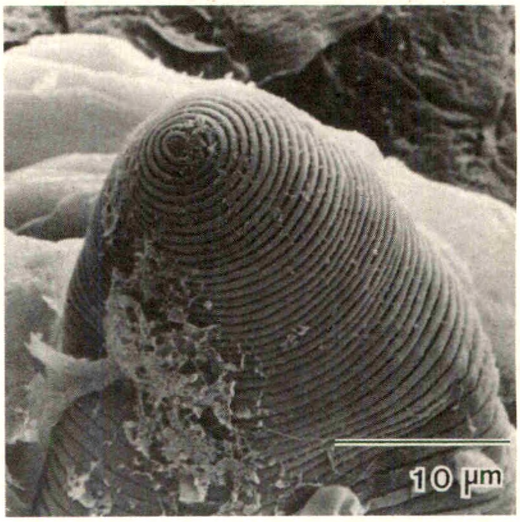


Fig. 2 (English and associates). Higher magnification of parasite showing classic inscriptions on the abdomen (× 2,320).

scanning electron microscopy.[1] We were interested to see if these parasites could also be isolated on the eyelid margin.

After a full-thickness resection for a shortening procedure of the lower eyelid of a 35-year-old woman, we took the specimen and placed it in 4% glutaraldehyde solution. This was then placed in 100% amylacetate and critically point dried. The sample was oriented on an aluminum stub, gold coated in a polaron sputter coater with 20 nm of gold, and viewed with a scanning electron microscope. After orientation of the eyelid under low power with the electron microscope, the tissue fragment was rotated to allow the eyelid margin to be examined in profile. Eyelashes were examined under higher magnifications, and acarid infestation of the cilium was recorded (Fig. 1).

The tail of the parasite *Demodex folliculorum* was observed as a dome-shaped object contiguous with an eyelash and protruding from the eyelid margin. It displayed the characteristic annular bands found on the abdomen. The peculiar pattern of these striations was observed under higher magnification (Fig. 2). Only the terminal portion of the abdomen of the parasite was identified.

Demodex brevis, the other species of the mite found in the eyelid, occurring in the meibomian glands and pilosebaceous complex, has a pointed caudate extremity and was not observed in our patient. The degree of infestation was not as heavy as that recorded in the facial skin studies in which multiple parasites were noted around hairs.

Reference

1. Crosti, C., Menni, S., Sala, F., and Piccinno, R.: Demodectic infestation of the pilosebaceous follicle. J. Cutan. Pathol. 10:257, 1983.

Capnocytophaga canimorsus as the Cause of a Chronic Corneal Infection

Marc D. de Smet, M.D., Chi Chao Chan, M.D., Robert B. Nussenblatt, M.D., and Alan G. Palestine, M.D.

Laboratory of Immunology, National Eye Institute.

Inquiries to Marc D. de Smet, M.D., Laboratory of Immunology, National Eye Institute, Bldg. 10, Rm. 10N202, Bethesda, MD 20892.

Dysgonic fermenter 2, a normal inhabitant of the dog's mouth, closely resembles the *Capnocytophaga* species found in humans. The latter have been shown to cause a chronic keratitis resembling a fungal or *Acanthamoeba* infec-

tion.[1,2] Dysgonic fermenter 2 is recognized as a cause of fulminant septicemia in patients without spleens or with alcoholic cirrhosis.[3] Infection frequently occurs after a dog bite or close contact with dogs or cats. The organism, a gliding gram-negative rod, is characterized by fastidious growth requirements. We treated a patient who developed a chronic deep corneal infection that required prolonged antibiotic therapy over several months because of this organism.

A 46-year-old veterinarian was struck on the right eye by a carious tooth while extracting it from a poodle with severe gingivitis. The patient sustained a superficial corneal laceration extending into the anterior stroma without any retained foreign body. He was treated with topical sulfacetamide.

While taking this regimen, the patient developed an intense photophobia and conjunctival injection. The site of injury was debrided and showed a staphylococcal species which was treated with topical fortified cefazolin (50 mg/ml) for two weeks. Visual acuity improved to R.E.: 20/25 with partial resolution of the photophobia. Visual acuity again deteriorated and the photophobia worsened within a month. A microscopic abscess growing *C. perfringens* was noted and debrided. The cornea was treated with topical fortified vancomycin hydrochloride. Visual acuity improved to R.E.: 20/25, only to worsen within one month to R.E.: 20/200 despite treatment.

Two months later and three days before admission to the National Eye Institute, visual acuity had decreased to counting fingers. The patient had an anterior chamber hypopyon. An aspirate of the anterior chamber did not show any organisms, but it did contain numerous polymorphonuclear cells. Slit-lamp examination disclosed marked conjunctival injection and an edematous cornea with an intact epithelium. Plaquelike deposits were seen at the level of the endothelium (Fig. 1). These deposits had well defined borders extending inward from the peripheral cornea. Smaller satellite lesions were also noted. A biopsy specimen taken from one of the lesions did not show any organisms but, once again, was characterized by a profusion of polymorphonuclear leukocytes. After five days, the anaerobic cultures disclosed a thin, nonspore-forming gram-negative rod measuring 1 to 3 μm. This was characterized as a dysgonic fermenter 2 organism (Fig. 2).

The patient was treated with a combination of intravenous cefazolin, 1 g every six hours, and topical eyedrops of cefazolin sodium, 50 mg/ml every hour. The patient was later switched to penicillin, 2,000,000 units intravenously every six hours and 100,000 U/ml topically, after he developed an allergic reaction to cefazolin. The eyedrops were continued for several months. Visual acuity improved to R.E.: 20/30 with a gradual lessening of the photophobia. The eyedrops were finally discontinued after the endothelial deposits and the photophobia had resolved.

Dysgonic fermenter 2 behaves in a way similar to other *Capnocytophaga* species. It is characterized by severe pain, decreased visual acuity,

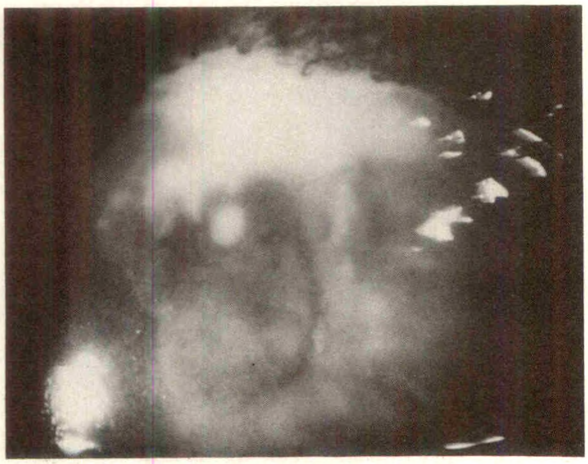


Fig. 1 (de Smet and associates). Slit-lamp appearance of the corneal subendothelial infiltrate one day postoperatively. Note the satellite lesions and the sharp demarcation of each lesion.

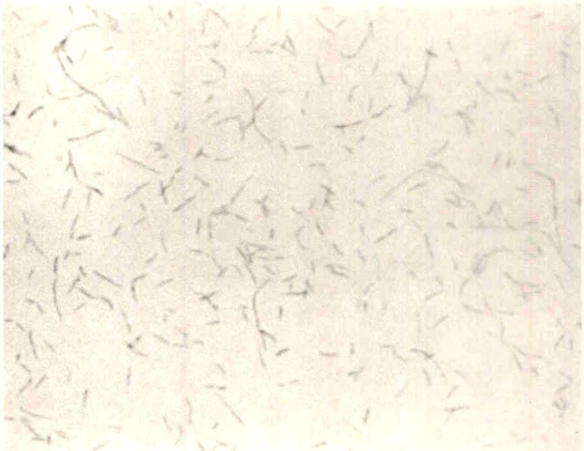


Fig. 2 (de Smet and associates). Appearance of the organism on Gram stain after seven days in culture (× 100). The organism is a gram-negative rod measuring 1 to 3 μm.

and slow, fastidious growth in culture. Anaerobic cultures must be maintained beyond the usual five days to detect this organism. This growth also occurs in vivo, which explains why the patient suffered three recurrences, each time with a deeper involvement. The bacterium, because of its slow growth, requires prolonged therapy for its eradication. Photophobia, possibly related to bacterial spread along corneal nerves, is probably the best indicator of persistent infection. Dysgonic fermenter 2 has a wide spectrum of antibiotic sensitivity. It is particularly sensitive to penicillin, clindamycin, and rifampin.[4] Dysgonic fermenter 2 corneal involvement can mimic fungal, acanthamebal, or stromal keratitis. One should suspect this organism in cases where a dog's oral flora may have infected the cornea.

References

1. Pamel, G. J., Buckley, D. J., Frucht, J., Krausz, H., and Feldman, S. T.: *Capnocytophaga* keratitis. Am. J. Ophthalmol. 107:193, 1989.

2. Heidemann, D. G., Pflugfelder, S. C., Kronish, J., Alfonso, E. C., Dunn, S. P., and Ullman, S.: Necrotizing keratitis caused by *Capnocytophaga ochracea.* Am. J. Ophthalmol. 105:655, 1988.

3. Brenner, D. J., Hollis, D. G., Fanning, G. R., and Weaver, R. E.: *Capnocytophaga canimorsus* sp. nov. (formerly CDC group DF-2), a cause of septicemia following dog bite, and *C. cynodegmi* sp. nov., a cause of localized wound infection following dog bite. J. Clin. Microbiol. 27:231, 1989.

4. Verghese, A., Hamati, F., Berk, S., Franzus, B., Berk, S., and Smith, J. K.: Susceptibility of dysgonic fermenter 2 to antimicrobial agents in vitro. Antimicrob. Agents Chemother. 32:78, 1988.

Microsporidia Infection of the Cornea in a Man Seropositive for Human Immunodeficiency Virus

Careen Y. Lowder, M.D.,
David M. Meisler, M.D.,
James T. McMahon, Ph.D.,
David L. Longworth, M.D.,
and Isobel Rutherford, M.D.

Departments of Ophthalmology (C.Y.L., D.M.M.), Pathology (J.T.M.), Infectious Disease (D.L.L.), and Microbiology (I.R.), Cleveland Clinic Foundation.

Inquiries to Careen Y. Lowder, M.D., Department of Ophthalmology, Cleveland Clinic Foundation, 9500 Euclid Ave., Cleveland, OH 44195-5024.

Microsporidia are obligate intracellular parasites that infect mammals, arthropods, fish, and birds. They rarely cause disease in humans.[1] Recently, however, microsporidia have been associated with hepatitis and enteritis in patients with the acquired immunodeficiency syndrome (AIDS).[2] We encountered a case of microsporidia corneal infection in an individual who was seropositive for human immunodeficiency virus antibodies.

A 30-year-old homosexual man with AIDS-related complex and known to be HIV-seropositive for three years, began having recurrent episodes of redness and crusting of both eyes in November 1988. Conjunctival cultures grew *Streptococcus viridans* and coagulase-negative staphylococcus. The patient was treated with the appropriate topical antibiotics without resolution of the condition. Ocular examination in February 1989 disclosed a best-corrected visual acuity of 20/25 in each eye. Slit-lamp examination showed marked bilateral conjunctival hyperemia, mixed follicular-papillary tarsal conjunctival reaction, and diffuse punctate epithelial keratopathy. Conjunctival cultures for bacteria, fungi, chlamydia, herpes simplex virus, herpes zoster virus, and adenovirus were negative. The patient's epithelial keratopathy worsened over the next three months, and visual acuity deteriorated to 20/60 in each eye (Fig. 1). In May 1989 corneal epithelium was scraped from the right eye and healed rapidly, but the epithelial keratopathy recurred.

Epithelial scrapings were submitted for cul-

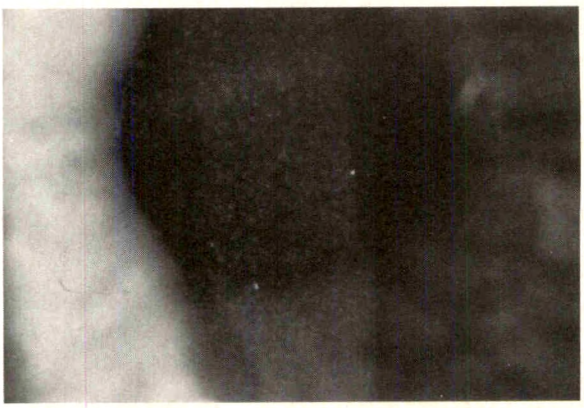


Fig. 1 (Lowder and associates). Slit-lamp photograph of punctate epithelial keratopathy.

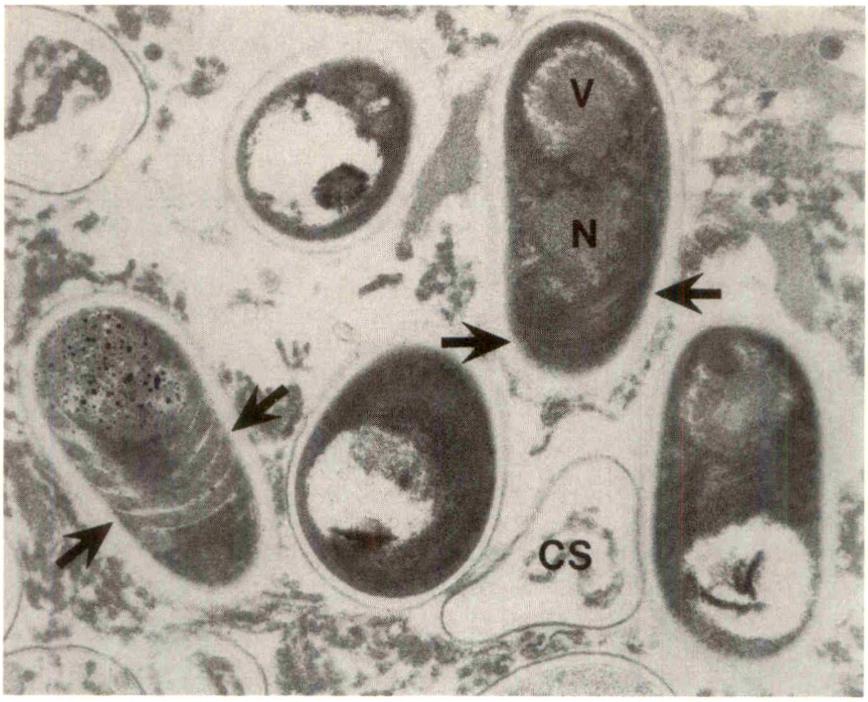


Fig. 2 (Lowder and associates). Transmission electron micrograph of intracellular microsporidial spores. Ultrastructural features of the organism include cell wall, coiled filament (arrows), polar vacuole (V), and single nucleus (N). Also present is a collapsed spore (CS) (× 24,000).

ture and microscopic studies. Cultures for bacteria, fungi, and retrovirus were negative. Light microscopy disclosed ribbons of corneal squamous epithelium. No inflammatory cells were observed. Gram-positive oval forms were seen within epithelial cells, and many of these inclusions had a vacuole and a densely staining nucleus. A single small periodic acid-Schiff stain-positive polar body was noted in many of the inclusions. Transmission electron microscopy demonstrated intracellular organisms, each measuring approximately 1 × 2 μm (Fig. 2). Most were surrounded by an 80-nm thick cell wall composed of a thick, inner electron-lucent zone and a thin, outer dense layer. Some organisms were surrounded only by the outer, dense layer and were interpreted as immature spore forms. A homogeneously fine granular nucleus and variably fibrillar to granular vacuole were noted in many organisms. Adjacent to the cell membrane, a cytoplasmic tubular filament measuring 0.1 μm in diameter formed six to eight coiled loops around the nucleus. This extended and attached to a dense plaquelike area on the cell membrane. The filament was often seen protruding from the organism, occasionally extending a considerable distance into the surrounding host cell cytoplasm. Numerous empty or collapsed cell walls, containing only remnants of cytoplasm and protruded filaments, were noted throughout the specimen. The histopathologic and ultrastructural findings confirmed the presence of the protozoan microsporidia.

We found two reports of microsporidiosis of the human cornea.[3,4] The infections resulted in severe keratitis in both cases. This led to perforation and enucleation of the eye in one case and penetrating keratoplasty in the other case. In our patient, the corneal infection appeared confined to the epithelium. The absence of an inflammatory response may be attributed to the patient's immunodeficient state.

Microsporidia are fastidious and difficult to recover in culture. The specific diagnosis of microsporidiosis is made by light and electron microscopic identification of the unique structural features of the organisms. There is no known therapy for microsporidium infections, although sulfonamides have shown some efficacy in vitro. Some patients treated with sulfa drugs have survived.[1]

Microsporidia should be suspected in persistent epithelial keratopathy with negative cultures in HIV-seropositive individuals. Epithelial scraping for light and electron microscopic evaluation is necessary for accurate diagnosis.

References

1. Shadduck, J. A., and Greeley, E.: Microsporidia and human infections. Clin. Microbiol. Rev. 2:158, 1989.
2. Shadduck, J. A.: Human microsporidiosis and AIDS. Rev. Infect. Dis. 11:203, 1989.
3. Ashton, N., and Wirasinha, P. A.: Encephalitozoonosis (Nosematosis) of the cornea. Br. J. Ophthalmol. 57:669, 1973.
4. Pinnolis, M., Egbert, P. R., Font, R. L., and Winter, F. C.: Nosematosis of the cornea. Arch. Ophthalmol. 99:1044, 1981.

Correspondence

Correspondence concerning recent articles or other material published in THE JOURNAL should be submitted within six weeks of publication. Correspondence must be typed double-spaced, on 8½ × 11-inch bond paper with 1½-inch margins on all four sides and should be no more than two typewritten pages in length.

Every effort will be made to resolve controversies between the correspondents and the authors of the article before publication.

Peripheral Retinal Angiomalike Lesion and Macular Pucker

EDITOR:

The article "Peripheral Retinal Angiomalike Lesion and Macular Pucker," by L. Laatikainen, I. Immonen, and P. Summanen (Am. J. Ophthalmol. 108:563, November 1989) described macular pucker formation in cases with peripheral vascular lesions. These cases are similar to a series of cases in which Williams and I found traction retinal detachments in combination with various retinal vascular diseases such as von Hippel-Lindau disease, exudative vitreoretinopathy, and Coats' disease.[1] The cases reported by Laatikainen, Immonen, and Summanen probably represent a lesser degree of the same entity we reported. We believed that the vascular tumors leak and cause reactive retinal glial proliferation resulting in preretinal membrane formation. These membranes can contract. They may cause puckers, depending on their location, or they may partially detach from the retina and cause traction retinal detachments.

Therapy has to be aimed first at elimination of the vascular lesions. Vitreous surgery will be considered to remove preretinal or vitreous membranes depending on the amount and type of proliferation.

ROBERT MACHEMER, M.D.
Durham, North Carolina

Reference

1. Machemer, R., and Williams, J. M., Jr.: Pathogenesis and therapy of traction detachment in various retinal vascular diseases. Am. J. Ophthalmol. 105:170, 1988.

Reply

EDITOR:

We did not discuss the pathogenesis of macular pucker in retinal vascular lesions in detail, but we agree with Dr. Machemer that preretinal membrane formation at the posterior pole was most likely initiated by the leaking vascular process in the peripheral retina. Our cases were less advanced than those reported by Machemer and Williams. No retinal detachment was noted, and the vitreous was clear in all eyes. Our cases stress the importance of careful evaluation of the peripheral retina in all cases with macular pucker.

Our aim in therapy was to treat the vascular lesion first, as was also proposed by Machemer. This seemed to stop membrane formation. Vitrectomy with membrane peeling was performed in two eyes after regression of the vascular changes because of significant visual disturbance. So far, no recurrent membranes or traction retinal detachments have been noted.

LEILA LAATIKAINEN, M.D.
Oulu, Finland
ILKKA IMMONEN, M.D.
PAULA SUMMANEN, M.D.
Helsinki, Finland

Familial Congenital Cornea Guttata With Anterior Polar Cataracts

EDITOR:

In the article, "Familial Congenital Cornea Guttata With Anterior Polar Cataracts," by E. I. Traboulsi and R. J. Weinberg (Am. J. Ophthalmol. 108:123, August 1989), the authors discuss autosomal dominant cornea guttata and anterior polar cataracts.

In the same issue, I described cornea guttata in two girls, not relatives, affected by an autosomal dominant neurocristopathy, mandibulofacial dysotosis.[1] I wonder if any of the 21 members of the family reported was investigated for neural crest disorders. Cornea guttata, Fuch's dystrophy, and Peter's anomaly are thought to depend on a neural crest defect.[2]

PAOLO NUCCI, M.D.
Milan, Italy

References

1. Nucci, P., Brancato, R., Carones, F., Alfarano, R., and Bianchi, S.: Mandibulofacial dysostosis and cornea guttata. Am. J. Ophthalmol. 108:204, 1989.
2. Bahn, C. F., Falls, H. F., Varley, G. A., Meyer, R. F., Edelhauser, H. F., and Bourne, W. M.: Classification of corneal endothelial disorders based on neural crest origin. Ophthalmology 91:558, 1984.

Reply

EDITOR:

None of the 21 members of the family described were specifically investigated for neural crest disorders. Medical histories, however, were obtained and showed no evidence of other inherited disorders within the family. As Dr. Nucci notes, the occurrence of corneal guttata may indeed depend on a neural crest defect. Bahn and associates[1] have suggested that cornea guttata may be a result of defects of final differentiation and function of cells of neural crest origin that occur late and, therefore, might explain the lack of additional neural crest-related conditions.

ELIAS I. TRABOULSI, M.D.
Arlington, Virginia
RICHARD J. WEINBERG, M.D.
Vienna, Virginia

Reference

1. Bahn, C. F., Falls, H. F., Varley, G. A., Meyer, R. F., Edelhauser, H. F., and Bourne, W. M.: Classification of corneal endothelial disorders based on neural crest origin. Ophthalmology 91:558, 1984.

BOOK REVIEWS

Edited by H. Stanley Thompson, M.D.

Contact Lenses. A Textbook for Practitioner and Student, ed. 3. Edited by Anthony J. Phillips and Janet Stone. London, Butterworths & Co., 1989. 1,017 pages, index, illustrated. $225

Reviewed by BARRY A. MALTZMAN
Jersey City, New Jersey

This is a technical, optometrist-oriented reference book that is a valuable volume for the student and for the experienced practitioner. As with any new textbook, there have been advances in technology that could not be included. Some of the subject matter discussed has already been revised and modified in recent journals and symposia.

The textbook, like a seasoned professor, provides historical background on the development of contact lens' materials and designs. The authors provide current technology interwoven with historical sketches that outline the innovative research and the steps that have led to this modern technology. Detailed didactic information is offered on ocular anatomy, physiology, and microbiology. Subjects that include more conceptual material, such as patient suitability and patient treatment, are written in an interesting and helpful fashion. The strength of these chapters is their organization and didactic presentation. The chapter on contact lens' solutions is especially refreshing because it is both up-to-date and provides extensive information on how these solutions work.

The chapters dealing with fitting contact lenses are practical and filled with detailed background material that enable the practitioner to understand the technology that is currently used. Specialty areas, such as extended-wear contact lenses and bifocal contact lenses, are topics in which research is creating new technology so rapidly that it is impossible for a textbook to be at the cutting edge.

There are, however, a few ideas that are stated with emphasis but supported by conflicting evidence. Some medical and surgical subjects, such as the use of contact lenses under abnormal conditions, postkeratoplasty, and postradial keratotomy contact lens wear, are difficult subjects for nonmedical contact lens specialists to understand completely. The chapter called "Refractive Changes After Wearing Contact Lenses" offers concepts that are not proven and could confuse the student or beginning practitioner. The highly technical subjects of manufacture, modification, and contact lens instrumentation are written in greater depth and detail than needed by most clinicians. Some of the ocular tests and photographs of instruments are outdated.

Nevertheless, this third edition of "Contact Lenses" is an organized and technical reference book. It is a valuable repository of the details of contact lens technology and of the history of the development of the modern contact lens. For these reasons alone it should be in every medical and ophthalmic library.

Guide to Clinical Preventive Services. An Assessment of the Effectiveness of 169 Interventions. Report of the U.S. Preventive Services Task Force. Edited by Michael Fisher. Baltimore, Williams & Wilkins, 1989. Softcover, 419 pages, index. $19.95

Reviewed by RONALD V. KEECH
Iowa City, Iowa

This text was developed by a 20-member task force of health professionals commissioned by the United States Department of Health and Human Services and reviewed by more than 300 experts. Recommendations for health practitioners on preventive interventions for 60 medical conditions are detailed. The recommendations are based on a review of current scientific evidence and make use of a standardized methodology.

One chapter provides minimum standards for a periodic health examination based on the leading causes of morbidity and mortality for the patient's age and sex, and the on effectiveness of intervention practices. Additional suggestions for high risk groups are also noted. Subsequent chapters address medical conditions such as coronary artery disease, breast cancer, hepatitis B, and depression. For each

condition, the authors discuss the impact of the disorder, the efficacy of the screening tests, the importance of early detection, and the recommendations of other experts. Based on this information, they offer specific recommendations for screening. A similar approach is also taken for preventive counseling on behaviors that may endanger health, such as tobacco use and overeating.

Screening measures are considered for two ocular conditions: diminished visual acuity and glaucoma. While the recommendations are more conservative than most ophthalmologists would prefer (for example, "it may be clinically prudent . . . to advise patients at high risk . . . to be tested periodically for glaucoma"), the discussion underscores the lack of data on the efficacy of these preventive practices and suggests avenues for future research.

Although intended for the primary-care practitioner, this book provides useful information for medical specialists interested in preventive medicine.

Books Received

Pneumatic Retinopexy. A Clinical Symposium. Edited by Paul E. Tornambe and W. Sanderson Grizzard. Chicago, Greenwood Publishing, 1989. 253 pages, index, illustrated. $69.95

Pneumatic retinopexy is an outpatient procedure that provides intraocular tamponade for specific retinal detachments. Gas is injected transconjunctivally into the vitreous and supplemented with laser photocoagulation, cryotherapy, or both. It promises to be an effective operation.

As with most new surgical procedures (as opposed to new drugs) the initiative appears to be in the hands of the surgeon and the controls are not government controls, they are aimed directly at the surgeon in the form of liability. Ten percent of this volume is devoted to this part of the problem.

The 1989 Year Book of Ophthalmology. Edited by Peter R. Laibson. Chicago, Year Book Medical Publishers, Inc., 1989. 238 pages, index, illustrated. $51.95

The Year Book editorial baton has been passed to Peter Laibson at Wills Eye Hospital, Philadelphia. Once again, it is a valuable bringing together of articles dimly remembered as "probably important," and otherwise hard to retrieve.

The Book List

Greer's Ocular Pathology, ed. 4. By David R. Lucas. Oxford, Blackwell Scientific Publications, 1989. 339 pages, index, illustrated. $99.95

Oculoplastic, Orbital, and Reconstructive Surgery, vol. 2. Orbit and Lacrimal System. Edited by Albert Hornblass. Baltimore, Williams & Wilkins, 1990. 1,543 pages, index, illustrated. $139.95

ABSTRACT DEPARTMENT

Edited by David Shoch, M.D.

Annals of Internal Medicine

Thyrotropin-secreting pituitary adenomas: clinical and biochemical heterogeneity. Gesundheit, N., Petrick, P. A., Nissim, M., Dahlberg, P., Doppman, J. L., Emerson, C. H., Braverman, L. E., Oldfield, E. H., and Weintraub, B. D. (Dr. Weintraub, Molecular, Cellular, and Nutritional Endocrinol. Branch, National Inst. of Diabetes and Digestive and Kidney Dis., National Inst. of Health, Bldg. 10, Room 8D14, Bethesda, MD 20892). Ann. Intern. Med. 111:827, 1989.

Hyperthyroidism usually results from primary thyroid disease and only rarely is secondary to inappropriate pituitary thyroid-stimulating hormone secretion. Most often patients with pituitary adenomas are misdiagnosed initially and treated for primary thyroid overactivity with radioactive iodine, surgery, or both. If the treatment induces hypothyroidism, these patients may experience accelerated tumor growth and increased morbidity from visual loss and anterior pituitary dysfunction.

The nine patients described here had thyroid-stimulating hormone secreting pituitary tumors, hyperthyroidism, and increased free thyroxine and triiodothyronine levels. The free alpha subunit, a tumor marker for neoplasms of gonadotropic or thyrotropic cell origin, was increased in all nine patients. The delay between the initial treatment of hyperthyroidism and the correct diagnosis of a pituitary neoplasm was 6.2 ± 4.8 years. No patient had proptosis either at the time of examination or in previous photographs. Seven of the nine patients developed macroadenomas. Two of these patients died. Four of the five remaining patients had a residual tumor and inappropriate thyroid-stimulating hormone secretion despite surgery and radiation therapy. In contrast, the two patients with microadenomas were clinically cured.

These cases emphasize the need for an earlier diagnosis of hyperthyroidism secondary to pituitary adenomas. These tumors have in common the oversecretion of thyroid-stimulating hormone (and its uncombined [free] alpha subunit) despite increased levels of free thyroid hormones. The authors recommend that thyroid-stimulating hormone be measured routinely in all patients with thyrotoxicosis, symmetrical goiter, and the absence of infiltrative ophthalmopathy or dermopathy to diagnose thyroid-stimulating hormone secreting pituitary tumors at an early stage before inappropriate antithyroid therapy. (2 figures, 2 tables, 45 references)—David Shoch

British Journal of Ophthalmology

Medical conditions underlying retinal vein occlusion in patients with glaucoma or ocular hypertension. Cole, M. D., Dodson, P. M., and Hendeles, S. (Torbay Hosp., Lawes Bridge, Torquay, Devon TQ2 7AA, U.K.). Br. J. Ophthalmol. 73:693, 1989.

Forty-three patients with glaucoma and 24 patients with ocular hypertension presenting with a retinal vein occlusion were medically assessed. The prevalence of systemic hypertension was 60.5% in those with glaucoma and 66.6% with ocular hypertension. The prevalence of hyperlipidaemia was 38.1% in those with glaucoma and 37.5% in those with ocular hypertension. These findings were compared with those from a carefully age-sex matched group of patients presenting with a retinal vein occlusion without evidence of glaucoma or ocular hypertension. There were no statistical differences between any of the groups (52.2% had systemic hypertension and 28.8% had hyperlipidaemia). There was also a strikingly high prevalence of systemic hypertension (89%) and hyperlipidaemia (55.5%) in nine of the patients who had evidence of a recurrent retinal vein occlusion associated with glaucoma, and these prevalence rates were strikingly similar to the rates in patients with recurrence but without glaucoma. The data suggest that glaucoma or ocular hypertension has a less prominent aetiological role in the development of a retinal vein occlusion than underlying medical causes and that full medical assessment is worthwhile. (7 tables, 40 references)—Authors' abstract

Is padding necessary after cataract extraction? Laws, D. E., Watts, M. T., Kirkby, G. R., and

Lawson, J. (Birmingham and Midland Eye Hosp., Church St., Birmingham B3 2NS, U.K.). Br. J. Ophthalmol. 73:699, 1989.

It is routine after cataract surgery to cover the eye with an eye pad, which is often combined with a protective shield usually having small perforations. To evaluate the worth of padding the eye after cataract surgery, the eyes of 22 patients were dressed with a petroleum jelly mesh eye pad and a plastic eye shield. The eye shield alone was used in 19 patients.

The incidence of postoperative positive bacterial cultures was about the same in the two groups. There was less discharge in the eyes with the shields only. Patients can see through the perforations in the shield, which would benefit patients without useful vision in the fellow eye. The authors encourage the dressing of eyes with a protective shield (preferably transparent) only. (2 tables, 6 references)—David Shoch

A fibrin sealant for perforated and preperforated corneal ulcers. Lagoutte, F. M., Gauthier, L., and Comte, P. R. M. (Hopital des Enfants, 168 Cours de l'Argonne, 33077 Bordeaux Cedex, France). Br. J. Ophthalmol. 73:757, 1989.

Perforated corneal ulcers present a special problem because frequently they occur in the presence of keratitis sicca where a graft is unlikely to be successful. Cyanoacrylates have been successful for small (1 mm) perforations, but in large perforations they may enter the anterior chamber and cause iritis and inflammation. More recently epikeratoplasty has been advised for the small perforations, but this requires the availability of material and is a much more elaborate procedure than using the sealant.

The authors report a successful treatment of nine perforations in eight patients using an organic material termed Tissel, manufactured in France. This material consists of two solutions, the first being an adhesive solution containing human fibrinogen, factor XIII, fibronectin, albumin, and a proteinase inhibitor of bovine origin. The second solution is freeze dried thrombin and a solution of calcium chloride. These two solutions are applied simultaneously through a single mixing needle, which is supplied with the material. The tissue adhesive takes about two minutes to set, after which the excess is trimmed. The trimming is easy because the excess does not adhere to the epithelium of healthy cornea where there is no collagen with which the fibrin crosslinks. A soft lens is then applied to limit any shearing forces. The material gradually absorbs, and the fibrin clot gradually degrades and is replaced by fibrous tissue. Because the material is of human origin, there is a possibility of virus transmission, particularly hepatitis virus and human immunodeficiency virus. To avoid such transmission, the plasma is subjected to radioimmunoassay and enzyme-linked immunosorbent assay. These tests are repeated on the plasma pools and on the final material itself. The finished product also undergoes thermoviroinactivation for 30 hours at 60 C. (3 figures, 23 references)—David Shoch

Diabetes

Effect of aspirin alone and aspirin plus dipyridamole in early diabetic retinopathy: a multicenter randomized controlled clinical trial. Damad Study Group. (Dept. Med., Hammersmith Hosp., Eva M. Kohner, Du Cane Rd., London W12 OHS, U.K.). Diabetes 38:491, 1989.

Four centers, two in France and two in the United Kingdom, took part in a double-blind, randomized, controlled clinical trial to test the effect of aspirin alone (330 mg three times daily) or aspirin in combination with dipyridamole (75 mg three times daily), on patients with early diabetic retinopathy. The criterion for effectiveness was the change in the number of microaneurysms present in the macular field as seen on fluorescein angiography over a three-year period. There was no significant difference between the aspirin group and the aspirin plus dipyridamole group. In the placebo group, there was a significant increase in the number of microaneurysms. There was a clear relationship between the worsening of ophthalmologic signs and the increase in microaneurysms. The authors believe that either aspirin alone or aspirin and dipyridamole significantly slows the progress of microaneurysms in early diabetic retinopathy. (13 figures, 26 references)—David Shoch

Pathogenesis of diabetic retinopathy. Engerman, R. L. (Dept. Ophthalmol., Univ. Wisconsin, 1300 Univ. Ave., Madison, WI 53706). Diabetes 38:1203, 1989.

Diabetic retinopathy involves anatomic changes in retinal vessels and neuroglia. The pathogenetic mechanism responsible for retinopathy is imperfectly understood, but much of the mechanism is apparently reproduced by experimental diabetes in animals and by chronic elevation of blood galactose in nondiabetic animals. The evidence that retinopathy is a consequence of excessive blood sugars and their sequelae is consistent with a demonstrated inhibition of retinopathy by strict glycemic control in diabetic dogs. However, retinopathy in the dog model has shown a tendency to resist intervention by strict control. Biochemical and pathophysiological sequelae of hyperglycemia possibly critical to the development of retinopathy in humans and animal models are being studied in many laboratories. Retinopathy occurs in experimental galactosemia in the absence of the renal hypertrophy, mesangial expansion, and glomerular obliteration typical of diabetes in humans and dogs, implying that retinopathy and nephropathy differ appreciably in pathogenesis. (1 figure, 20 references)—Author's abstract

Prevalence and risk factors of diabetic retinopathy in non-Hispanic whites and Hispanics with NIDDM. San Luis Valley Diabetes Study. Hamman, R. F., Mayer, E. J., Moo-Young, G. A., Hildenbrandt, W., Marshall, J. A., and Baxter, J. (Dept. Preventive Med. and Biometrics and Dept. of Ophthalmology, Box C-245, Univ. of Colorado School of Med., Denver, CO 80262). Diabetes 38:1231, 1989.

A recent report from the San Antonio Heart Study showed that Mexican Americans were at greater risk for severe diabetic retinopathy (DR) than non-Hispanic Whites. To compare the prevalence of DR between non-Hispanics and Hispanics in southern Colorado, 279 people with non-insulin-dependent diabetes mellitus were identified, and retinal photographs identified the presence and severity of retinopathy. The worse eye was used to classify the severity of DR for each patient. Ninety percent of the subjects (166 Hispanics and 85 non-Hispanic Whites) were classified by retinopathy level. The duration-adjusted prevalence of any DR was 41.8% in Hispanics and 54.1% in non-Hispanic Whites. Severe DR (preproliferative and proliferative) occurred in 18.5% of the Hispanics and 21.3% of the non-Hispanic Whites. The odds ratio for any DR, comparing Hispanics with non-Hispanic Whites adjusted for other risk factors, was 0.40 (95% confidence interval = 0.21, 0.76). Other risk factors for the presence of any retinopathy included use of exogenous insulin, increased duration of diabetes, younger age at diagnosis, increased glycosylated hemoglobin level, and increased systolic blood pressure. These data suggest that, compared with non-Hispanic Whites, Hispanics in Colorado may be at decreased risk for DR. (1 figure, 4 tables, 32 references)—Authors' abstract

Journal of Clinical Oncology

A prospective ophthalmic evaluation of patients with acute myeloid leukemia: correlation of ocular and hematologic findings. Karesh, J. W., Goldman, E. J., Reck, K., Kelman, S. E., Lee, E. J., and Schiffer, C. A. (Dept. Ophthalmol., Univ. Maryland Hosp., 22 S. Greene St., Baltimore, MD 21201). J. Clin. Oncol. 7:1528, 1989.

Over a two-year period, 56 patients with newly diagnosed, untreated acute myeloid leukemia had complete ocular examinations. Two patients were excused from the study because of pre-existing diabetic retinopathy and one patient refused to participate. Twenty-eight (53%) study patients had retinopathy at the time of their initial examinations. Nineteen had both cotton wool spots and various types of retinal hemorrhages. Seven had hemorrhages alone and two had cotton wool spots alone. Three patients with retinal hemorrhages also had optic nerve edema without clinical evidence of central nervous system leukemia.

The occurrence of ocular findings was unrelated to age, sex, classification of leukemia, or pretreatment leukocyte count. The patients with retinopathy had significantly lower platelet counts than those without retinopathy. The presence of retinopathy was unrelated to therapeutic response, but there was complete resolution of all ocular findings in patients who survived the induction phase of therapy. Prophylactic platelet transfusions to maintain platelet counts at greater than 20,000/μl may have contributed to the rapid resolution and absence of long-term sequelae. (2 tables, 16 references)—David Shoch

Journal of Rheumatology

Antibodies to iris and retina detected in sera from patients with juvenile rheumatoid arthritis with iridocyclitis by indirect immunofluorescence studies on human eye tissue. Uchiyama, R. C., Osborn, T. G., and Moore, T. L. (St. Louis Univ. School of Med., Div. Rheumatol., R212 Doisy Hall, 1402 S. Grand Blvd., St. Louis, MO 63104). J. Rheumatol. 16:8, 1989.

Sera from 12 patients with juvenile rheumatoid arthritis (JRA) with active iridocyclitis were incubated with frozen, sectioned, whole human eye tissue. Antibodies were detected using fluorescein conjugated goat $F(ab')_2$ antibody to human IgG by immunofluorescent microscopy. Immunofluorescence was determined on tissue from the iris, retina, and 3 portions of the ciliary body. Sera of patients with JRA with iridocyclitis were compared to sera from patients with JRA with and without antinuclear antibodies (ANA) and healthy children. An increased frequency of antibody to the human iris was seen with sera of patients with JRA with iridocyclitis compared to healthy children's sera. A higher frequency of antibody was also noted to human retina in sera of patients with JRA with iridocyclitis compared to patients without ANA and healthy children. No increased frequency of antibody was detected to ciliary body. Sera of 7 patients with JRA with iridocyclitis were also compared during a time of inactive eye disease to a time of active disease. No difference in binding to eye tissue was detected at times of inactive disease compared to controls. Our results demonstrate the presence of antibody to iris and retina by immunofluorescence in the sera of patients with JRA with iridocyclitis. (4 figures, 2 tables, 16 references)—Authors' abstract

Neurosurgery

Laser-assisted reconstruction of the oculomotor nerve: experimental study on the feasibility of cranial nerve repair. Seifert, V., and Stolke, D. (Neurosurgical Clin. Med. School of Hannover, Konstanty-Gutschowstr. 8, 3000 Hannover 61, West Germany). Neurosurgery 25:579, 1989.

The CO_2 laser has been used for the precise incision of neural tissue and the atraumatic vaporization of poorly vascularized tumors of the central nervous system. The ability of the CO_2 laser to bond organic tissue by its thermal effect has led to the development of CO_2 lasers working to experimentally perform vascular and peripheral nerve anastomosis. To evaluate the usefulness of this technique for cranial nerve repair, the authors exposed the oculomotor nerve in 12 adult cats from its exit at the brain stem to its entry into the rudimentary cavernous sinus. The nerve was cut about in the middle of the course. In six of the cats, the cut ends were welded together with a CO_2 laser (80 to 90 mW and a 150-μm spot size). In the control group of six animals, nerve reconstruction was performed either with fibrin glue or by simple nerve reapproximation.

Twelve weeks later the oculomotor nerve was again explored and removed in one piece. No dehiscence of the welded nerve was present. All six animals with laser-assisted repair of the oculomotor nerve recovered various degrees of function. Pupillary reaction to light was almost complete in four animals, and there was partial recovery in two. Of the three cats in which nerve reconstruction was attempted with fibrin glue, partial recovery of the oculomotor nerve was observed in one animal only; no recovery occurred in the three animals in the control group in which the divided nerve was left without a reconstructive procedure. A similar technique might be used on transsected facial nerves. (5 figures, 39 references)—David Shoch

New England Journal of Medicine

The cardinal manifestations of Bardet-Biedl syndrome, a form of Laurence-Moon-Biedl syndrome. Green, J. S., Parfrey, P. S., Harnett, J. D., Farid, N. R., Cramer, B. C., Johnson, G., Heath, O., McManamon, P. J., O'Leary, E., and Pryse-Phillips, W. (Div. Nephrology, Health Sci. Ctr., Memorial Univ. of Newfoundland, St. John's, NF A1B 3V6, Canada). N. Engl. J. Med. 321:1002, 1989.

To determine the interfamilial and intrafamilial variation in the expression of the Bardet-Biedl syndrome (a form of Laurence-Moon-Biedl syndrome), we looked for the five recognized features of the disorder (retinal dystrophy, obesity, polydactyly, mental retardation, and hypogonadism), plus possible renal mani-

festations, in some or all of 32 patients with this disorder.

All 28 patients examined had severe retinal dystrophy, but only 2 had typical retinitis pigmentosa. Polydactyly was present in 18 of 31 patients, but syndactyly, brachydactyly, or both were present in all. Obesity was present in all but 1 of 25 patients. Only 13 of 32 patients were considered mentally retarded. Scores on verbal subtests of intelligence were usually lower than scores on performance tasks. Seven of eight men had small testes and genitalia, which was not due to hypogonadotropism. All 12 women studied had menstrual irregularities, and 3 had low serum estrogen levels (1 of these had hypogonadotropism, and 2 had primary gonadal failure). The remaining women who were of reproductive age had endocrinologic evidence of reproductive dysfunction. Diabetes mellitus was present in 9 of 20 patients. Renal structural or functional abnormalities were universal ($n = 21$), and three patients had end-stage renal failure.

We conclude that the characteristic features of Bardet-Biedl syndrome are severe retinal dystrophy, dysmorphic extremities, obesity, renal abnormalities, and (in male patients only) hypogenitalism. Mental retardation, polydactyly, and hypogonadism in female patients are not necessarily present. (2 figures, 5 tables, 37 references)—Authors' abstract

Use of corticosteroids to prevent progression of Graves' ophthalmopathy after radioiodine therapy for hyperthyroidism. Bartalena, L., Marcocci, C., Bogazzi, F., Ranicucci, M., Lepri, A., and Pinchera, A. (Istituto di Endocrinologia, Univ. Pisa, Viale del Tirreno 64, 56018 Tirrenia-Pisa, Italy). N. Engl. J. Med. 321:1349, 1989.

We studied the effects of radioiodine treatment of hyperthyroidism due to Graves' disease on Graves' ophthalmopathy and the possible protective role of corticosteroids. Between June 1985 and June 1988, 26 patients were randomly assigned to treatment with radioiodine alone (group 1) and 26 to treatment with this agent and concomitant administration of systemic prednisone for four months (group 2). The initial dose of prednisone was 0.4 to 0.5 mg per kilogram of body weight for one month; the drug was gradually withdrawn over the next three months. All patients were evaluated at 3-month intervals for 18 months after they underwent radioiodine therapy. Ocular changes were assessed with the ophthalmopathy index; patients with moderate-to-severe changes (scores ≥ 4) were excluded from the study.

Before treatment, 10 patients in group 1 and 5 in group 2 had no evidence of ophthalmopathy; in none of them did ocular symptoms appear after radioiodine therapy. Among the patients in group 1 with an initial ophthalmopathy index ≥ 1, ocular disease worsened in 56 percent (mostly involving soft-tissue changes and extraocular-muscle function) and did not change in 44 percent. In contrast, ophthalmopathy improved in 52 percent and did not change in 48 percent of group 2. The mean ophthalmopathy index increased from 1.5 to 3.0 in group 1 ($P < 0.005$) and decreased from 2.2 to 1.3 in group 2 ($P < 0.05$).

We conclude that systemic corticosteroid treatment prevents the exacerbations of Graves' ophthalmopathy that occur after radioiodine therapy in a substantial proportion of patients with hyperthyroidism who have some degree of ocular involvement before treatment. (2 figures, 33 references)—Authors' abstract

Prednisone and cyclosporine in the treatment of severe Graves' ophthalmopathy. Prummel, M. F., Mourtis, M., Berghout, A., Krenning, E. P., van der Gaag, R., Koornneef, L., and Wiersinga, W. M. (Dept. Endocrinol., F5-258, Academic Med. Ctr., Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands). N. Engl. J. Med. 321:1353, 1989.

It is uncertain what is the most appropriate medical therapy for patients with severe Graves' ophthalmopathy. Therefore, we carried out a single-blind, randomized clinical trial to compare the efficacy of prednisone with that of cyclosporine in 36 patients who had been euthyroid for at least two months. The two groups, each consisting of 18 patients, were similar in age, sex, and the duration and severity of ophthalmopathy.

The initial dose of cyclosporine was 7.5 mg per kilogram of body weight per day, and that of prednisone was 60 mg per day, which was subsequently tapered to 20 mg per day. During the 12-week treatment period, 11 prednisone-treated and 4 cyclosporine-treated patients responded to therapy (61 percent vs. 22 percent;

P = 0.018); response was manifested by decreases in eye-muscle enlargement and proptosis and improved visual acuity and total and subjective eye scores. There were no differences at base line between the patients who later responded and those who did not. Prednisone was tolerated less well than cyclosporine.

After 12 weeks, patients who did not respond were treated for another 12 weeks with a combination of cyclosporine and a low dose of prednisone. Among the 9 patients who initially received prednisone, the addition of cyclosporine resulted in improvement in 5 (56 percent); among the 13 patients who received cyclosporine initially, 8 (62 percent) improved after the addition of prednisone. Combination therapy was better tolerated than prednisone treatment alone.

We conclude that single-drug therapy with prednisone is more effective than cyclosporine in patients with severe Graves' ophthalmopathy. The combination can be effective in patients who do not respond to either drug alone. (5 tables, 26 references)—Authors' abstract

NEWS ITEMS

Send News Items to
American Journal of Ophthalmology
435 N. Michigan Ave., Suite 1415
Chicago, IL 60611

The Journal invites readers to submit announcements concerning meetings, postgraduate courses, lectures, honors, and appointments. Each item must be typed double-spaced on bond paper with 1½-inch margins. Only one news item should be submitted on each page. Announcements concerning meetings and courses must contain the title, location, dates, sponsors, and address required for additional information. Each item must not exceed 75 words in length and be prepared in narrative, not outline, form. Announcements of meetings and courses must be received at least four months before the event.

The Hospital for Sick Children: Jack Crawford, M.D., Paediatric Ophthalmology Conference

The Hospital for Sick Children: Jack Crawford, M.D., Paediatric Ophthalmology Conference will be held March 30 and 31, 1990, in Toronto, Ontario. For further information, write Peggy Wood, Department of Ophthalmology, Hospital for Sick Children, 555 University Ave., Toronto, Ontario, Canada M5G 1X8; telephone (416) 598-6503.

Humana Hospital-Lexington: Clinical Advances in Treatment of Retina, Vitreous and Uveal Diseases for the Practicing Ophthalmologist

Humana Hospital-Lexington will sponsor a course, Clinical Advances in Treatment of Retina, Vitreous and Uveal Diseases for the Practicing Ophthalmologist, April 6 and 7, 1990, at Marriott's Griffin Gate Resort, Lexington, Kentucky. For further information, write Karen Heidorn, Humana Hospital-Lexington, 150 N. Eagle Creek Dr., Lexington, KY 40509.

Manhattan Eye, Ear, & Throat Hospital: Contact B and A Scan Diagnostic Ultrasonography Course

The Manhattan Eye, Ear, & Throat Hospital: Contact B and A Scan Diagnostic Ultrasonography Course will be held April 7, 1990, in New York City. For further information, write Francine Leinhardt, Course Coordinator, Manhattan Eye, Ear, & Throat Hospital, 210 E. 64th St., New York, NY 10021; telephone (212) 838-9200, ext. 2776.

Ohio State University: 33rd Annual Postgraduate Symposium in Ophthalmology—Current Concepts in Corneal Disease

The Ohio State University: 33rd Annual Postgraduate Symposium in Ophthalmology—Current Concepts in Corneal Disease will be held March 2 and 3, 1990, at the Hyatt on Capitol Square, Columbus, Ohio. For further information, telephone Ohio State University Center for Continuing Medical Education at (800) 492-4445 or (614) 292-4985.

Pittsburgh Ophthalmology Society: 26th Annual Spring Meeting

The Pittsburgh Ophthalmology Society: 26th Annual Spring Meeting will be held March 30 and 31, 1990, at the Vista International Hotel, Pittsburgh. For further information, write Pat Williamson, Pittsburgh Ophthalmology Society, 2545 Mosside Blvd., Monroeville, PA 15146; telephone (412) 243-8845.

University of Toronto: 32nd Annual Departmental Research Meeting and Tenth Clement McCulloch Lecture

The University of Toronto: 32nd Annual Departmental Research Meeting and Tenth Clement McCulloch Lecture will be held April 6, 1990, at the Addiction Research Foundation Auditorium, Toronto. For further information, write Dr. G. E. Trope, Department of Ophthalmology, Toronto General Hospital, Eaton Building, 5-306, Toronto, Ontario, Canada M5G 2C4; telephone (416) 340-3580.

Université de Montréal: La Cataracte

Université de Montréal: La Cataracte, a course sponsored by Les Entretiens Ophtalmologiques de l'Université de Montréal, will be held April 5 and 6, 1990, at the Bonaventure Hilton Hotel in Montreal, Quebec. For further information, write Les Entretiens Ophtalmologiques de l'Université de Montréal (E.O.U.M.), 2250 est Boul. St.-Joseph, Montreal, Quebec, Canada H2H 1G3; telephone (514) 525-3888 or 524-6420.

Utah Ophthalmological Society: Annual Winter Ski Meeting

The Utah Ophthalmological Society: Annual Winter Ski Meeting will be held Feb. 20–23,

1990, at Doubletree Hotel, Salt Lake City, Utah. For further information, write Carol Leavitt, Director of Communications, Utah Ophthalmological Society, 540 E. Fifth S., Salt Lake City, UT 84102; telephone (801) 355-7477.

Washington National Eye Center: Automated Perimetry Course

The Washington National Eye Center: Automated Perimetry Course will be held April 27 and 28, 1990, at the Washington Hospital Center, Washington, D.C. For further information, write Penelope A. Helfgott, WNEC, Suite 6B-13, 110 Irving St. N.W., Washington, DC 20010.

Wills Eye Hospital: 42nd Annual Conference

The Wills Eye Hospital: 42nd Annual Conference will be held March 29–31, 1990, at the Adam's Mark Hotel in Philadelphia. For further information, write Jeanne Coughlin, Meeting Manager, 1621 Norristown Rd., Maple Glen, PA 19002; telephone (215) 322-8950.

The Fight For Sight Research Division of the National Society to Prevent Blindess: 1989–1990 Awards

In September 1988, Fight For Sight, Inc., became the research division of Prevent Blindness. The program is now administered by Pamela S. Peters, Director of Program Services for the National Society to Prevent Blindness. Arthur M. Silverstein chairs the Research Scientific Advisory Board, composed of Arthur H. Neufeld, Robert B. Nussenblatt, Steven M. Podos, Harris Ripps, and Melvin L. Rubin.

Scientific research awards approved for funding during the year 1989–1990 include 17 grants-in-aid; 14 postdoctoral research fellowships; 15 student fellowships; continued support to four Fight For Sight pediatric eye clinics; and two Fight For Sight citations for outstanding achievement in ophthalmic and vision research.

Grants-in-Aid

George Jesse Baldo, Ph.D., Department of Physiology and Biophysics, State University of New York, Stony Brook, NY. "Biophysical and Molecular Properties of Lens Gap Junctions," supported by the Hearst Foundation, $11,000.

Michael H. Chaitin, Ph.D., Bascom Palmer Eye Institute, University of Miami School of Medicine, Miami, FL. "Actin Filament Polarity in Developing Outer Segments of Normal and rds Mutant Mice," $10,000.

James Wendell Doyle, Ph.D., Eye Research Institute, Harvard Medical School, Boston, MA. "Effect of Retinoids on Retinal Pigment Epithelium Growth and Differentiation," $9,000.

Federico Gonzalez-Fernandez, M.D., Ph.D., Department of Pathology, University of Virginia School of Medicine, Charlottesville, VA. "Rat Interstitial-Retinol Binding Protein: Molecular Cloning and Gene Expression," in Memory of Mary E. and Alexander P. Hirsch, $8,500.

Sharon C. Gross, M.D., Ph.D., Department of Ophthalmology, University of Maryland School of Medicine, Baltimore, MD. "Isolation of Endogenous Corneal Inhibitor of Collagenase Synthesis," $9,500.

James Douglas Hayashi, M.D., Department of Ophthalmology, Washington University School of Medicine, St. Louis, MO. "Effect of Light Upon HSV-1 Retinitis," $8,000.

Glenn Jay Jaffe, M.D., Department of Ophthalmology, Duke University, Durham, NC. "Effect of Hypoxia on Retinal Neovascularization," $11,000.

Ruth Deborah Lipman, Ph.D., Human Nutrition Research Center on Aging, Tufts University, Boston, MA. "Prevention of After-Cataract Formation," $9,000.

Jan Marie McDonnell, M.D., Departments of Ophthalmology and Pathology, University of Southern California School of Medicine, Los Angeles, CA. "Conjunctival Infection With Human Papilloma Virus," $11,000.

Shizuo Mukai, M.D., Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, MA. "Development of Monoclonal Antibodies to the Natural Product of the Retinoblastoma Gene," in Tribute to Bob Hope, $11,000.

Maria Musarella, M.D., Departments of Ophthalmology and Genetics, Hospital for Sick Children, Toronto, Ontario. "Cloning of a Gene for X-linked Retinitis Pigmentosa," $11,000.

Stephen C. Pflugfelder, M.D., Department of Ophthalmology, University of Miami School of Medicine, Miami, FL. "Evaluation of the Pathogenesis of Lacrimal Gland Lymphocytic Destruction in Primary Sjogren's Syndrome Patients," $6,600.

Joel S. Schuman, M.D., and Mark A. Latina, M.D., Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, MA. "Modulation of Tenon's Fibroblast Function by Timolol," in Memory of Mary E. and Alexander P. Hirsch, $11,000.

Susan Lynn Semple-Rowland, Ph.D., Department of Neuroscience, University of Florida, Gainesville, FL. "Biochemical Characterization

of Proteins Affected by the Retinal Degeneration (*rd*) Mutation in Chick," $10,700.

Harold John Sheedlo, Ph.D., Department of Anatomy, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, NC. "Mechanisms of PRC Rescue in an Animal Model of Inherited Retinal Dystrophy by RPE Cell Transplantation," in Tribute to Bob Hope, $3,850.

Andrew J. Sweatt, Ph.D., Departments of Ophthalmology and Anatomy, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, NC. "Ultrastructural and Cytochemical Studies of the Retina-RPE Interface During *in vitro* Induction of Photoreceptor Outer Segment Disk Shedding," $8,000.

Lucy Hwa-Yue Young, M.D., Ph.D., Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, MA. "Immunoregulation of Ocular Malignant Melanoma in an Experimental Animal Model," $11,000.

Postdoctoral Fellowships

Seerat Aziz, D.O., School of Optometry, University of California, Berkeley, CA (Jay M. Enoch, Ph.D., Sponsor). "Study of Visual Field Defects in Tourette Syndrome," $12,000.

Kathleen Boesze-Battaglia, Ph.D., Department of Biochemistry, State University of New York at Buffalo, Buffalo, NY (Arlene Albert, Ph.D., Sponsor). "Studies of Rhodopsin Phosphorylation in Bovine Rod Outer Segments," $12,000.

Sandra Lee Craner, Ph.D., Department of Neurobiology, Anatomy and Cell Science, University of Pittsburgh, Pittsburgh, PA (Raymond D. Lund, Ph.D., Sponsor). "Cortical Activity Mediated by Retinal Transplants," in Memory of Silas Adelsheim, $12,000.

Donald Bruce Dixon, Ph.D., Department of Ophthalmology, University of California, San Francisco, CA (David R. Copenhagen, Ph.D., Sponsor). "Mechanisms of Glutamatergic Transmission in the Retina," $10,000.

Andrew Marc Garfinkle, M.D., Ph.D., Department of Ophthalmology, McGill University, Montreal, Quebec (R. Sipehia, Ph.D., Sponsor). "Synthetic Corneal Inlays," $12,000.

Jan Peter Gierow, Ph.D., Department of Physiology and Biophysics, University of Southern California, Los Angeles, CA (Austin K. Mircheff, Ph.D., Sponsor). "Class II Histocompatibility Molecules in Rat Exorbital Lacrimal Gland," $12,000.

Kathrin Herrmann, Ph.D., Department of Neurobiology, Stanford University School of Medicine, Stanford, CA (Carla J. Shatz, Ph.D., Sponsor). "The Function of the Subplate in the Development of the Geniculocortical Projection in the Cat," $12,000.

Nobuo Kouyama, Ph.D., Department of Neurobiology and Anatomy, University of Texas Medical School, Houston, TX (David W. Marshak, Ph.D., Sponsor). "Peptidergic Bipolar Cells in the Retina of the Macaque Monkey," $12,000.

Motonobu Nishimura, M.D., Department of Pharmacology, New York Medical College, Valhalla, NY (Michal Laniado Schwartzman, Ph.D., Sponsor). "12(R)HETE, Corneal Function and Intraocular Pressure," $12,000.

Akihiko Oohira, M.D., The Wilmer Ophthalmological Institute, Johns Hopkins University School of Medicine, Baltimore, MD (David S. Zee, M.D., Sponsor). "Function of Extraocular Muscle Proprioceptors," in Memory of Dr. Hermann M. Burian and wife, Gladys, $12,000.

Deborah Ann Orel-Bixler, Ph.D., Department of Physiological Optics, University of California, Berkeley, CA (Gunilla Haegerstrom-Portnoy, O.D., Ph.D., Sponsor). "Photorefraction, Acuity and Contrast Sensitivity of the Multihandicapped Patient," $12,000.

Sukumar Pal, Ph.D., The Wilmer Ophthalmological Institute, The Johns Hopkins University, School of Medicine, Baltimore, MD (Judith Whittum-Hudson, Ph.D., Sponsor). "Analysis of Local and Systemic Immune Responses After Immunization With Two Major Outer Membrane Proteins of *Chlamydia trachomatis*," $12,000.

Yaron Solomon Rabinowitz, M.D., The Wilmer Ophthalmological Institute, Johns Hopkins University School of Medicine, Baltimore, MD (Irene H. Maumenee, M.D., Sponsor). "Gene Linkage Analysis in Familial Keratoconus," in Honor of Dr. Charles A. Perera, $12,000.

Julio Anibal Rimarachin, M.D., Department of Physiology, New York Medical College, Valhalla, NY (Mary E. Gerritsen, Ph.D., Sponsor). "Growth Control of Corneal Endothelium," $12,000.

Student Fellowships

Dipali V. Apte, Department of Physiology and Biophysics, University of Illinois, Urbana, IL (Dr. Thomas G. Ebrey, Sponsor). "Metabolism of the Single Toad Retina Using Phosphor-

us-31 Nuclear Magnetic Resonance Spectroscopy," $1,200.

Norma Bacilious, Department of Ophthalmology, Mount Sinai Medical Center, New York, NY (Penny Asbell, M.D., Sponsor). "Intraocular Pressure and the Intrastromal Corneal Ring," in Memory of Norma Cohen, $800.

Shamik Bafna, W. K. Kellogg Eye Center, University of Michigan Medical School, Ann Arbor, MI (H. Kaz Soong, M.D., Sponsor). "Galvanotropic/Taxis Response of Corneal Epithelial Cells to DC Electric Fields," in Honor of Neil Weisman, $1,200.

Andrew Ethan Budson, Department of Neurology, Harvard Medical School, The Children's Hospital, Boston, MA (Stuart A. Lipton, M.D., Ph.D., Sponsor). "Retinal Ganglion Cell Killing by AIDS Virus Envelope Protein Is Mediated by Ca^{2+} Current and Prevented by Ca^{2+} Channel Antagonists," funded by a grant from The Burroughs Wellcome Fund, $1,200.

Juliana Seungmi Paik, Department of Biochemistry, State University of New York at Buffalo, Buffalo, NY (Arlene Albert, Ph.D., Sponsor). "Effect of Cholesterol on Rhodopsin Activation of PDEase Cascade," funded by a grant from The Burroughs Wellcome Fund, $1,200.

Kurt Bryan Repke, Department of Anatomy, University of Medicine and Dentistry of New Jersey, Newark, NJ (Lois K. Laemle, Ph.D., Sponsor). "Effect of Retinal Dystrophy on the Lateral Geniculate Nucleus in the Rat," $800.

Mark Filios Rounds, Ophthalmology Research Laboratory, University of Rochester Medical Center, Rochester, NY (Seymour Zigman, Ph.D., Sponsor). "Visual Enhancement Using Short Wavelength Light Filters," supported by the James Thurber Memorial Fund, $800.

Douglas Thomas Saladik, Department of Biology, Temple University, Philadelphia, PA (Joel B. Sheffield, Ph.D., Sponsor). "Production of Fab Fragments of Monoclonal Antibody 1-1C8 C1 16," supported by the James Thurber Memorial Fund, $1,200.

Eric Ian Sbar, Department of Biology, Temple University, Philadelphia, PA (S. Robert Hilfer, Ph.D., Sponsor). "Basal Lamina and Optic Cup Formation," $1,200.

Gary Stewart Schwartz, Eye Research Institute, Harvard Medical School, Boston, MA (Mark A. Latina, M.D., Sponsor). "Effect of Timolol on Tenon's Capsule and Scleral Fibroblast Proliferation," in Honor of Elsie K. Sloate, $1,200.

Ann Marie Skoczenski, Center for Visual Science, University of Rochester, Rochester, NY (Richard N. Aslin, Ph.D., Sponsor). "Role of Spatial Summation in Infant Vernier Acuity," $1,200.

Gene R. Stoner, The Salk Institute, San Diego, CA (Thomas D. Albright, Ph.D., Sponsor). "Neuronal Activity Underlying Motion Perception of 2-D Patterns," $1,200.

George Hiroshi Tanaka, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, MA (Hong-Ming Cheng, Ph.D., Sponsor). "C-13 NMR Spectroscopy of Corneal Endothelial Bicarbonate Transport," funded by a grant from Canon, U.S.A., Inc., $1,200.

Leslie Jeanne Weil, Department of Ophthalmology, Emory University, Atlanta, GA (Paul Sternberg, Jr., M.D., Sponsor). "Protective Effect of Blue Light (<515nm) Attenuating Upon Glutathione Depleted Cultured Human Retinal Pigment Epithelial Cells," in Tribute to Bob Hope, $800.

James Matthew Weisz, Department of Ophthalmology, Columbia University, New York, NY (Peter Gouras, M.D., Sponsor). "Retinoid Metabolism in the Cultured Retinal Pigment Epithelium of an Abyssinian Cat Model of Progressive Retinal Atrophy," supported by the Albert G. and Herman B. Mosler Memorial Fund, $1,200.

Service Projects

Columbia-Presbyterian Medical Center, New York City, NY, Howard M. Eggers, M.D., Director, $5,000.

Eye Institute of New Jersey, Newark, NJ, Anthony R. Caputo, M.D., Director, $14,750.

Children's Hospital of the University of Pittsburgh, Pittsburgh, PA, Albert W. Biglan, M.D., Director, $3,500.

Wills Eye Hospital, Philadelphia, PA, Joseph Calhoun, M.D., Director, $14,485

1988 Fight For Sight Citations

For Achievement in Basic Research: Awarded to Joyce Tombran-Tink, B.S., and Lincoln V. Johnson, Ph.D., Department of Anatomy and Cell Biology, University of Southern California, Los Angeles, CA. "Neuronal Differentiation of Retinoblastoma Cells Cultured in Medium Conditioned by Human RPE Cells," $500.

For Achievement in Clinical Research: Awarded to Tian-Sheng Hu, M.D., Jia-Liang Zhao, M.D., Department of Ophthalmology, Peking Union Medical College, Beijing, China;

Qu Shen, M.D., The Tibet Eye Study Group, Department of Ophthalmology, People's Hospital of Tibet, Lhasa, China; and Robert D. Sperduto, M.D., National Eye Institute, National Institutes of Health, Bethesda, MD. "Age-Related Cataract in the Tibet Eye Study (TES)," $500.

Minnesota Academy of Ophthalmology: 21st Annual William L. Benedict Lecture

The Minnesota Academy of Ophthalmology presented the 21st Annual William L. Benedict Memorial Lecture at its meeting Jan. 12, 1990. Philip Brunelle, conductor for Garrison Keillor and frequent radio personality, was the guest speaker. Dr. Benedict was president of the Ophthalmic Publishing Company at the time of his death in 1969.

Personals

Denis M. O'Day

Denis M. O'Day has been named the Michael J. Hogan Professor of Ophthalmology at Vanderbilt University School of Medicine, Nashville, Tennessee. The professorship honors the late Dr. Hogan, who was professor and chairman of the Department of Ophthalmology, University of California, San Francisco, during Dr. O'Day's training there.

Roger F. Steinert

Roger F. Steinert has been appointed director of the Cornea Consultation Service at the Massachusetts Eye and Ear Infirmary in Boston.

MARCH 15

1990

AMERICAN JOURNAL OF OPHTHALMOLOGY

Monthly since 1884

• ORIGINAL ARTICLES

Choroidal Melanomas With Serous Macular Detachments
Erie, Robertson, Mieler

Age-related Macular Changes
Feeney-Burns, Burns, Gao

The Pattern Electroretinogram in Diabetes
Prager, Garcia, Mincher, Mishra, Chu

Familial Retinal Cavernous Hemangioma
Bottoni, Canevini, Canger, Orzalesi

Helicoid Peripapillary Chorioretinal Degeneration
Brazitikos, Safran

Posterior Vitreous Cyst
Steinmetz, Straatsma, Rubin

Branch Retinal Vein Occlusion
Weinberg, Dodwell, Fern

Trabeculectomy and Suture Lysis
Melamed, Ashkenazi, Glovinski, Blumenthal

Glaucoma in Oculo-Dento-Osseous Dysplasia
Traboulsi, Parks

Blepharoptosis Repair
Spoor, Kwitko

Gas-Permeable Scleral Contact Lenses
Schein, Rosenthal, Ducharme

Recurrence of Posterior Polymorphous Dystrophy
Boruchoff, Weiner, Albert

Povidone-Iodine and Ophthalmic Disinfection
Benevento, Murray, Reed, Pepose

***Listeria monocytogenes* Keratitis**
Zaidman, Coudron, Piros

• PERSPECTIVES

Competition and Ophthalmology
Noreika

• LETTERS TO THE JOURNAL

Anterior segment ischemia after trifluridine treatment
Shearer, Bourne

Superior oblique paresis and Brown's syndrome
Neely, Ernest, Mottier

Acquired Brown's syndrome after peribulbar anesthesia
Erie

Echography in restrictive motility
Ruttum, Lloyd, Lewandowski

Needle-stick injury and donor eyes
van Rens, Reed

***Capnocytophaga* keratitis**
Ticho, Urban, Safran, Saggau

Sebaceous gland carcinoma of the eyelid
Grossniklaus, Swerlick, Solomon

Retinoblastoma associated with holoprosencephaly
Desai, Shields, Shields, Donoso, Wagner

Floppy eyelid syndrome in a child
Eiferman, Gossman, O'Neill, Douglas

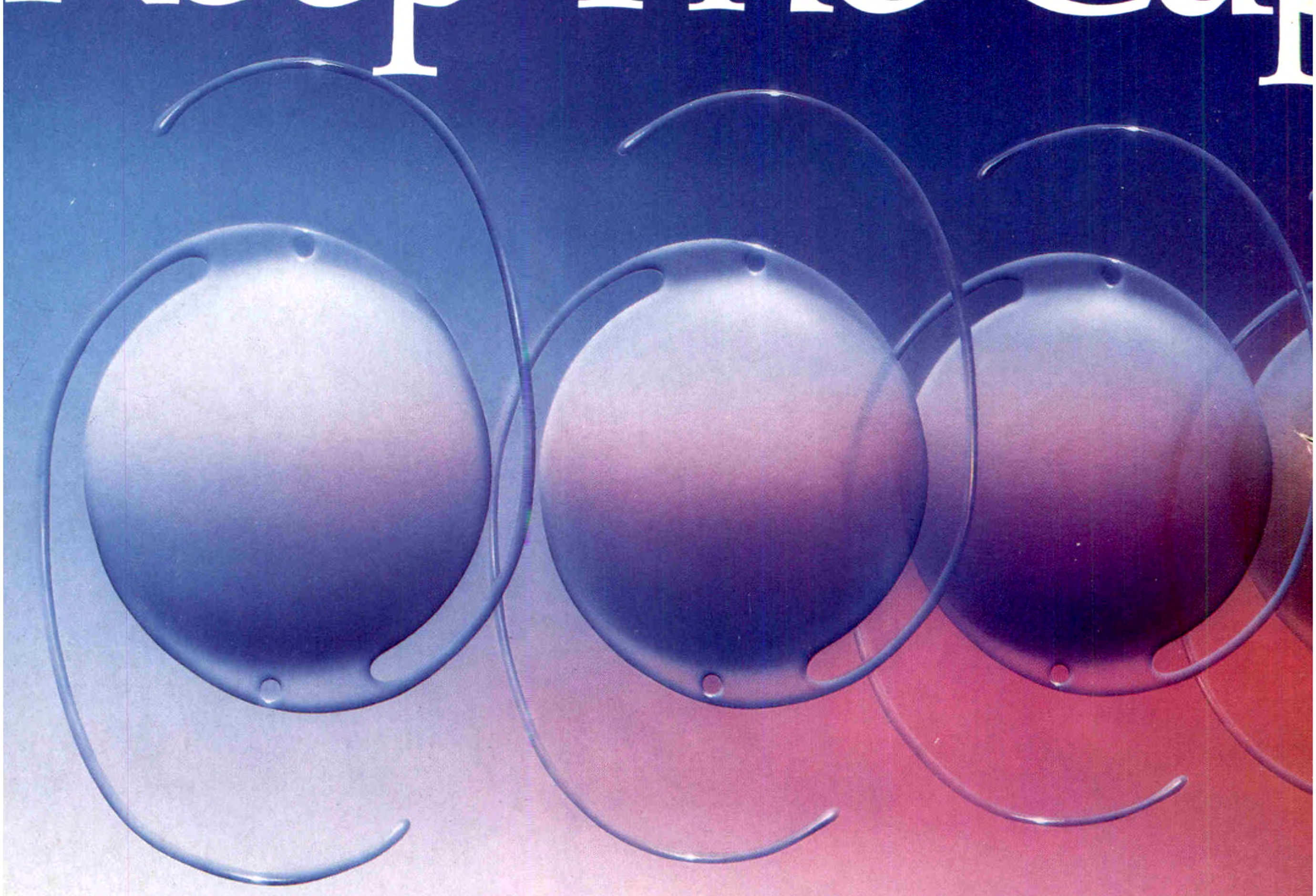
Sarcoid choroidopathy
Brod

Fiberoptic manipulators and illuminators
Michels, Sidikaro

Instrument for subretinal fluid drainage
Michels, Sidikaro

AJO®

Keep The Ca



Lens before implantation shown with proper orientation

By conforming, not deforming.

Bag Conformity and Centration. The two features of CILCO® cantilever loop single-piece IOLs that provide for better capsular fit.

Their proprietary haptic designs allow these lenses to accommodate to the size of the capsular bag. This conformity can eliminate the unequal zonular stress and the capsular bag distortion that can occur with an exceptionally long haptic, or unforgiving haptic design. The ability to accommodate also decreases the likelihood of a haptic overextending the anterior capsular flap and displacing into the sulcus.

Our unique haptic designs result in uniform radial forces that automatically center the optic. These gentle forces of centration also restore the natural shape of the capsular bag. This is achieved by providing an effective 360 degrees of radial stretch. And, this stretch helps to eliminate capsular wrinkles, a primary pathway for posterior capsule opacification.

Manufactured from lathe-cut, high molecular weight PMMA, these lenses exhibit superior memory. Thus, they preserve the angulation that minimizes the risk of

Now with binocular vision testing capabilities

Newest testing system provides a more precise way to measure stereopsis, suppression, associated phoria, and fixation disparity at distance.

Faster, more accurate *and* more versatile than any other vision tester.

Mentor's high speed, liquid crystal shutter glasses may be added to all B-VAT II and B-VAT II-SG models.

Mentor's B-VAT® Series Video Acuity Testers

B-VAT II — instantly displays 9 different optotypes including one or more lines of Snellen letters, Landolt rings, children's symbols, tumbling E's and HOTV as well as astigmatic clock dial, red-green, etc. A touch of the button changes the display from single to multiple characters in sizes from 20/15 to 20/300.

B-VAT II-SG — all of B-VAT II's capabilities plus! B-VAT II-SG incorporates an advanced sinusoidal gratings technique to perform the *contrast sensitivity* testing many eye care specialists find helpful for evaluating functional vision, documenting the need for cataract surgery, and detecting early pathology.

BINOCULAR VISION SYSTEM BVS™ — stereo acuity tests include familiar circle test and a unique random dot pattern with a tumbling E. Hand controller displays stereo acuity in seconds of arc, fixation disparity in minutes of arc and associated phoria. Two suppression tests include choice of 6 optotypes. Interaction bars for testing crowding effect are included.

To order and/or arrange a demonstration,
please write or call toll free:
1-800-992-7557 (National) 1-617-871-6950 (Collect in MA)

MENTOR O&O INC.

Binocular Vision System Patent Pending

AJO® AMERICAN JOURNAL OF OPHTHALMOLOGY®

ISSN 0002-9394 March 1990 Series 3, Vol. 109, No. 3

TABLE OF CONTENTS

ORIGINAL ARTICLES

Presumed small choroidal melanomas with serous macular detachments with and without surface laser photocoagulation treatment
Jay C. Erie, Dennis M. Robertson, and William F. Mieler 259

Age-related macular changes in humans over 90 years old
Lynette Feeney-Burns, Robert P. Burns, and Chun-Lan Gao 265

The pattern electroretinogram in diabetes
Thomas C. Prager, Charles A. Garcia, Caroline A. Mincher, Jasleen Mishra, and Hshuan-Ho Chu 279

Twin vessels in familial retinal cavernous hemangioma
Ferdinando Bottoni, Maria P. Canevini, Raffaele Canger, and Nicola Orzalesi 285

Helicoid peripapillary chorioretinal degeneration
Periklis D. Brazitikos and Avinoam B. Safran 290

Posterior vitreous cyst
Robert L. Steinmetz, Bradley R. Straatsma, and Melvin L. Rubin 295

Anatomy of arteriovenous crossings in branch retinal vein occlusion
David Weinberg, David G. Dodwell, and Steven A. Fern 298

Tight scleral flap trabeculectomy with postoperative laser suture lysis
Shlomo Melamed, Isaac Ashkenazi, Joseph Glovinski, and Michael Blumenthal 303

Glaucoma in oculo-dento-osseous dysplasia
Elias I. Traboulsi and Marshall M. Parks 310

Blepharoptosis repair by fascia lata suspension with direct tarsal and frontalis fixation
Thomas C. Spoor and Geoffrey M. Kwitko 314

A gas-permeable scleral contact lens for visual rehabilitation
Oliver D. Schein, Perry Rosenthal, and Christopher Ducharme 318

Recurrence of posterior polymorphous corneal dystrophy after penetrating keratoplasty
S. Arthur Boruchoff, Mark J. Weiner, and Daniel M. Albert 323

The sensitivity of *Neisseria gonorrhoeae, Chlamydia trachomatis,* and herpes simplex type II to disinfection with povidone-iodine
William J. Benevento, Patrick Murray, Charles A. Reed, and Jay S. Pepose 329

***Listeria monocytogenes* keratitis**
Gerald W. Zaidman, Philip Coudron, and Judy Piros 334

PERSPECTIVES

Competition and ophthalmology
Joseph C. Noreika 340

LETTERS TO THE JOURNAL

Severe ocular anterior segment ischemia after long-term trifluridine treatment for presumed herpetic keratitis. *Douglas R. Shearer and William M. Bourne,* **346. Combined superior oblique paresis and Brown's syndrome after blepharoplasty.** *Kimberly A. Neely, J. Terry Ernest, and Marianne Mottier,* **347. Acquired Brown's syndrome after peribulbar anesthesia.** *J. C. Erie,* **349. Echography in the diagnosis of restrictive motility caused by severe myopia.** *Mark S. Ruttum, Mary Ann Lloyd, and Michael F. Lewandowski,* **350. Elimination of the risk of needle-stick injury in handling donor eyes.** *Erik van Rens and John W. Reed,* **351. *Capnocytophaga* keratitis associated with poor dentition and human immunodeficiency virus infection.** *Benjamin H. Ticho, Robert C. Urban, Jr., Marc J. Safran, and David D. Saggau,* **352. IgA and complement immunofluorescent pattern in sebaceous gland carcinoma of the eyelid.** *Hans E. Grossniklaus, Robert A. Swerlick, and Alvin R. Solomon,* **353. Retinoblastoma associated with holoprosencephaly.** *Vinay N. Desai, Carol L. Shields, Jerry A. Shields, Larry A. Donoso, and Rudolph S. Wagner,* **355. Floppy eyelid syndrome in a child.** *Richard A. Eiferman, M. Douglas Gossman, Kelly O'Neill, and Craig H. Douglas,* **356. Presumed sarcoid choroidopathy mimicking birdshot retinochoroidopathy.** *Roy D. Brod,* **357. Shadow- and reflex-free use of combined fiberoptic manipulators and illuminators in vitreous surgery.** *Mark Michels and Yossi Sidikaro,* **358. A new instrument for ab interno drainage of subretinal fluid.** *Mark Michels and Yossi Sidikaro,* **360.**

CORRESPONDENCE

Glaucomalike disks without increased intraocular pressure or visual field loss. *Jeffrey W. Kalenak,* **361. Reply.** *Goji Tomita, Takenori Takamoto, and Bernard Schwartz,* **361. Pars plana vitrectomy in the management of dislocated posterior chamber lenses.** *Timothy G. Murray, Gary W. Abrams, and John Stanley,* **362. Reply.** *Randy V. Campo, Kelly D. Chung, and Ray T. Oyakawa,* **362. Automated perimetry, tonometry, and questionnaire in glaucoma screening.** *Alfred Sommer,* **362.**

(Table of Contents continued on Advertising Page 8)

AJO® AMERICAN JOURNAL OF OPHTHALMOLOGY®

ISSN 0002-9394 March 1990 Series 3, Vol. 109, No. 3

TABLE OF CONTENTS *(continued from Advertising page 6)*

BOOK REVIEWS

A Color Atlas of Ptosis. A Practical Guide to Evaluation and Management (Jonathan J. Dutton). *Reviewed by John A. Long,* **364. Oculoplastic and Orbital Emergencies (Edited by John V. Linberg).** *Reviewed by Gary S. Weinstein,* **364. Myopia Surgery. Anterior and Posterior Segments (Edited by Frank B. Thompson).** *Reviewed by Mark J. Mannis,* **365. Developments in Ophthalmology, vol. 20. Graves' Ophthalmopathy. Developments on Diagnostic Methods and Therapeutical Procedures (Edited by C. Renate Pickardt and Klaus Peter Boergen).** *Reviewed by Steven E. Feldon,* **365. Accountability in Research. Policies and Quality Assurance (Edited by Adil E. Shamoo), 366. Atlas of Ocular Motility (Leonard B. Nelson and Robert A. Catalano), 366. Developments in Ophthalmology. Ultrastructure of the Conjunctival Epithelium (Klaus-Peter Steuhl), 366. Differential Diagnosis of Hereditary Vitreoretinopathy (A. Spallone), 366. Inherited and Environmentally Induced Retinal Degenerations (Edited by Matthew M. LaVail, Robert E. Anderson, and Joe G. Hollyfield), 366. Introduction to Ophthalmology, ed. 3 (John Parr), 367. Manual of Retinal Surgery (Edited by Andrew J. Packer), 367. Microsurgery of the Eye. Main Aspects (Edited by S. N. Fyodorov), 367. Vision and the Brain. The Organization of the Central Visual System (Edited by Bernard Cohen and Ivan Bodis-Wollner), 367. The Visual Fields. Text and Atlas of Clinical Perimetry, ed. 6 (David O. Harrington and Michael V. Drake), 367.**

MEETINGS 368

ABSTRACTS 372

CORRECTION 375

NEWS ITEMS 376

CLASSIFIEDS . . . . Begins on Advertising 49

COPYRIGHT TRANSFER . . . . Advertising 10

CURRENT ISSUE SUMMARIES . . . . Begins of Advertising 14

INSTRUCTIONS TO AUTHORS . . . . Advertising 37

NEW PRODUCTS AND SERVICES . . . . Begins on Advertising 32

ADVERTISING INDEX . . . . Advertising 53

AMERICAN JOURNAL OF OPHTHALMOLOGY®

VOLUME 109 NUMBER 3 MARCH, 1990

Presumed Small Choroidal Melanomas With Serous Macular Detachments With and Without Surface Laser Photocoagulation Treatment

Jay C. Erie, M.D., Dennis M. Robertson, M.D., and William F. Mieler, M.D.

We reviewed the records of 22 patients (22 eyes) who had presumed small choroidal melanomas associated with a serous macular detachment. In 13 eyes, the tumor surface was treated with laser photocoagulation to reattach the retina and improve vision. After photocoagulation, the retina reattached in 11 eyes (85%), and the visual acuity improved in eight eyes (62%), returning to 20/25 or better in six eyes (46%). Twelve of the tumors (92%) that received surface photocoagulation grew after treatment. Seven of these tumors (54%) developed a collar-button configuration and showed evidence of basal expansion. Of the nine tumors that did not receive surface photocoagulation, seven (78%) eventually grew, but none developed a collar-button configuration. Surface photocoagulation applied to a growing melanoma appears to increase the likelihood of tumor extension through Bruch's membrane in a collar-button configuration. The impact of such growth on tumor metastasis is unknown.

Accepted for publication Dec. 20, 1989.

From the Department of Ophthalmology, Mayo Clinic and Mayo Foundation, Rochester, Minnesota (Drs. Erie and Robertson), and the Department of Ophthalmology, Medical College of Wisconsin, Milwaukee, Wisconsin (Dr. Mieler). This study was funded in part by a grant from Research to Prevent Blindness, Inc.

Reprint requests to J. C. Erie, M.D., Mayo Clinic, 200 First St. S.W., Rochester, MN 55905.

THE EFFECTS of choroidal melanomas on the overlying retina have been well described.[1] Subretinal fluid can occur with some of these lesions and may involve the macula, resulting in decreased vision. Erie and Robertson,[2] in their study of small choroidal melanomas, concluded that the presence of an associated serous macular detachment indicated that the tumor was likely to demonstrate significant growth within two years. Gass[3] reached a similar conclusion in his study of larger tumors suspected to be melanomas.

The study of Erie and Robertson[2] as well as that of Gass[3] documented the resolution of serous macular detachments after laser photocoagulation applied over the tumor surface. Erie and Robertson concluded that surface photocoagulation was a reasonable treatment to promote improvement in vision while the eye was kept under surveillance for possible tumor growth. The question arose, however, whether the growth pattern, particularly the development of a collar-button configuration, was influenced by the surface photocoagulation. After their study, Erie and Robertson chose to follow up similar cases of small choroidal melanomas with serous macular detachments that had not undergone surface photocoagulation.

In the present study we reviewed the experience of the Mayo Clinic and the Medical College of Wisconsin with respect to small choroidal melanomas associated with serous macular

detachments that were observed with and without surface laser photocoagulation treatment in a nonrandomized fashion.

Subjects and Methods

We reviewed the records of all patients with presumed small choroidal melanomas (4 to 10 mm in greatest base dimension and 1.5 to 3.0 mm in height as measured by standardized A-scan echography) who had been referred to the Mayo Clinic and the Medical College of Wisconsin between January 1974 and May 1988. Only those patients who had small choroidal melanomas associated with a serous macular detachment were included in the study. Patients' records were reviewed for visual acuity, size of tumor at initial examination, color photographic and fluorescein angiographic appearance, character of surface photocoagulation treatment if given, and changes during follow-up.

Results

Twenty-two patients had a serous macular detachment and a presumed small choroidal melanoma in one eye. Their ages at the time of diagnosis ranged between 20 and 73 years, with a mean age of 53 years. Fourteen patients were men and eight were women. Thirteen tumors involved the right eye, and nine tumors involved the left eye. All patients had reduced vision in the involved eye. Their visual acuities ranged from 20/30 to 5/200 at the time of initial examination. The mechanism of visual loss in all patients was believed to be related to subretinal fluid extending from the melanotic choroidal tumor into the macula. At initial examination, the size of the choroidal tumors had a mean basal diameter of 5.5 mm (range of largest diameter, 4 to 9 mm) and a mean thickness of 2.2 mm (range, 1.5 to 3 mm).

In 13 patients, we treated the tumor surface with argon laser photocoagulation. The photocoagulation was applied to focal areas of exudative leakage as indicated by angiography (Table 1). The photocoagulation burns were 500 mm in size with power sufficient to cause mild blanching of the retinal pigment epithelium. In some instances, there was mild diffuse leakage over the entire tumor surface, which necessitated nearly confluent treatment. No attempt was made to treat the choroidal tumor tissue beneath the retinal pigment epithelium.

After initial photocoagulation, there was resorption of subretinal fluid in 11 of 13 patients (85%). In eight of these patients, visual acuity improved two or more lines in Snellen acuity. The mean duration of improved vision was 13

TABLE 1

PATIENTS WITH SMALL CHOROIDAL MELANOMAS TREATED WITH LASER PHOTOCOAGULATION

PATIENT NO., AGE (YRS), SEX	TUMOR DIMENSIONS (MM)		VISUAL ACUITY		INTERVAL (MOS)		FINAL OUTCOME	FOLLOW-UP (MOS)
	INITIAL	AFTER GROWTH	INITIAL	FINAL	INITIAL ASSESSMENT TO TUMOR GROWTH	FINAL LASER TO TUMOR GROWTH		
1, 41, F	4 × 5 × 2	5 × 8 × 3.5*	20/40	20/20	24	14	Enucleation (mixed cell)	120
2, 52, M	7 × 8 × 2	7 × 8.5 × 3.5*	20/50	20/30	18	16	I 125 brachytherapy	54
3, 43, M	9 × 6 × 3	10 × 8 × 4	20/40	20/25	26	26	I 125 brachytherapy	120
4, 69, M	6 × 4 × 2	9 × 6 × 4	20/60	20/25	50	45	I 125 brachytherapy	108
5, 63, M	6 × 4 × 2	8 × 5 × 7*	20/60	20/25	34	15	Enucleation (mixed cell)	78
6, 47, M	4.5 × 6 × 2	8 × 5 × 7*	20/50	20/25	9	4	Enucleation (mixed cell)	42
7, 44, F	8 × 6 × 2	12 × 7.5 × 2.5	20/60	20/60	29	9	Enucleation (spindle B)	78
8, 73, F	5 × 3 × 2	No change	20/70	20/70	—	—	Observation	60
9, 26, F	3 × 4 × 1.9	6 × 7 × 4*	20/100	5/200	11	11	Enucleation (mixed cell)	14
10, 59, M	4 × 4 × 2.25	7 × 7 × 3.75*	20/60	20/40	8	8	I 125 brachytherapy	18
11, 63, M	5 × 3.5 × 1.5	5 × 4 × 6*	20/50	20/60	30	30	Enucleation (mixed cell)	96
12, 64, M	7 × 5 × 2.25	7.5 × 5.5 × 2.5	20/70	20/25	14	14	Observation	27
13, 54, F	5 × 5 × 1.7	6 × 6 × 2.4	20/50	20/70	11	11	Observation	108

*Collar-button growth pattern observed.

months (range, two to 24 months). In three patients, vision did not improve despite resolution of subretinal fluid.

There was a recurrence of subretinal fluid involving the macula in nine of the 11 patients who initially responded to photocoagulation. All received additional photocoagulation. There was resolution of subretinal fluid in six of these patients, and visual acuity improved to 20/25 or better in five. The mean duration of improved vision after the second photocoagulation treatment was 11 months (range, one to 16 months). Three patients did not respond to the second photocoagulation treatment. Thus, with one or two photocoagulation treatments, fluid resorption occurred in 11 of 13 eyes (85%), and vision improved in eight eyes (62%), with six eyes (46%) returning to a visual acuity of 20/25 or better.

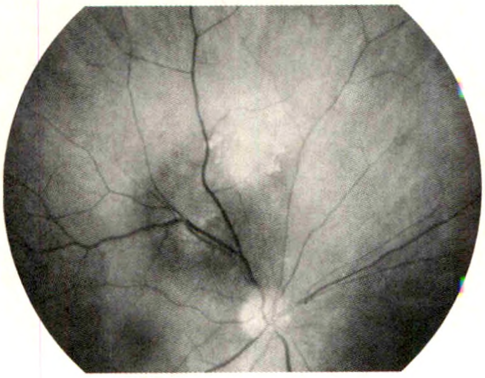
The mean follow-up period of the 13 tumors receiving photocoagulation was 5.8 years (range, 13 months to ten years). During this time, 12 of the 13 tumors (92%) had documented growth. This was characterized by expansion of the base dimension by a mean of 2.0 mm (range, 0.5 to 4.0 mm) and an increase in elevation by a mean of 1.9 mm (range, 0.2 to 5.0 mm). Although the tumors had documented growth both laterally and in height, seven (54%) developed a collar-button growth pattern (Figure). The mean duration between the initial examination and when growth was first noted was 23 months (range, eight to 50 months). The mean duration between the final laser treatment and when growth was first noted was 12 months (range, four to 45 months). The only tumor without documented growth was followed up for five years until the patient died of unknown causes.

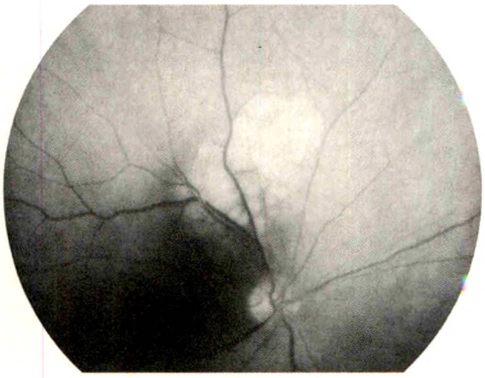
Ten of the 12 eyes that had tumors with documented growth eventually received further treatment. Six eyes underwent enucleation, and four had iodine 125 brachytherapy. The remaining two eyes had tumors that showed only minimal growth and are still being followed up. Histologic examination of the enucleated specimens showed five tumors to be mixed cell choroidal melanomas and one to be a spindle B choroidal melanoma. Twelve patients are alive and free of recognizable metastases at the last follow-up visit. One patient died of unknown causes but had no recognizable metastases at the last follow-up visit. The mean follow-up of these patients whose tumors were treated with brachytherapy or enucleation was 73 months (range, 14 to 120 months).

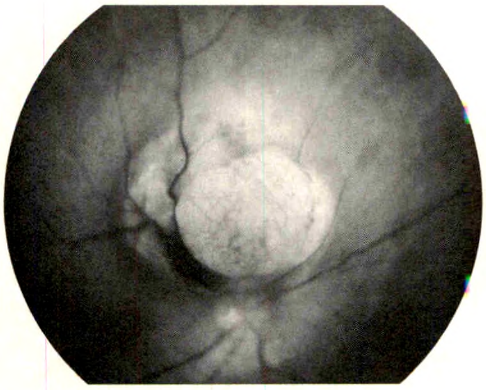
Nine patients with small choroidal melanomas and associated serous macular detachments did not receive laser therapy (Table 2). Initial visual acuity ranged from 20/30 to 5/200. Visual acuity did not improve or eventually deteriorated in all nine patients during the observation period. The mean follow-up was 24.4 months (range, five to 104 months). All patients were followed up until significant growth was noted or a minimum of one year if no growth had been observed. During this time, seven of nine tumors (78%) had documented growth, which was characterized by expansion of the base dimension by a mean of 1.1 mm (range, 0.5 to 3.5 mm) and an increase in elevation by a mean of 1.0 mm (range, 0.7 to 1.4 mm). The mean duration between the initial examination and when growth was first noted was 11.3 months (range, four to 26 months). None of the seven tumors with documented growth demonstrated a collar-button configuration. One of the tumors that did not grow has been followed up for 19 months. In the other instance, the eye that had the tumor was enucleated one month after initial examination.

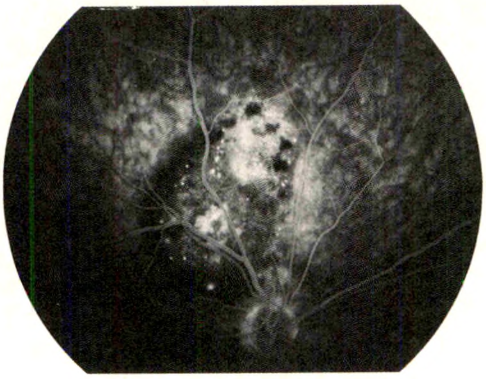
Six of the seven eyes that had growing tumors not treated with photocoagulation eventually received treatment. Five eyes were enucleated, and one eye received iodine 125 brachytherapy. Histologic examination of the enucleated specimens showed all five tumors to be mixed-cell choroidal melanomas. All nine patients were alive and free of recognizable metastases at their last follow-up visit. The mean follow-up of these patients whose eyes were treated with brachytherapy or enucleation was 17 months (range, seven to 24 months). Including the series of eyes in which photocoagulation was performed, the mean follow-up of all patients whose eyes were treated with brachytherapy or enucleation was 36 months (range, seven to 120 months).

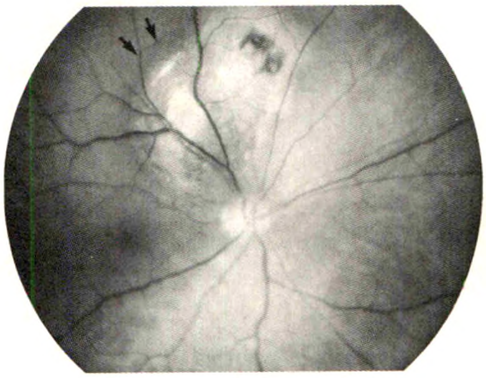
Although the presumed small choroidal melanomas in this series were treated in a nonrandomized fashion, those tumors that received photocoagulation were similar in size and in amount of subretinal fluid to those tumors that did not receive photocoagulation. Those choroidal tumors treated with surface laser photocoagulation had an initial mean largest diameter of 6.0 mm (range, 4.0 to 9.0 mm) and a mean thickness of 2.1 mm (range, 1.5 to 3.0 mm). Those tumors that did not receive laser therapy had an initial mean largest diameter of 6.2 mm (range, 4.0 to 9.0 mm) and a mean thickness of 2.3 mm (range, 1.6 to 2.9 mm).











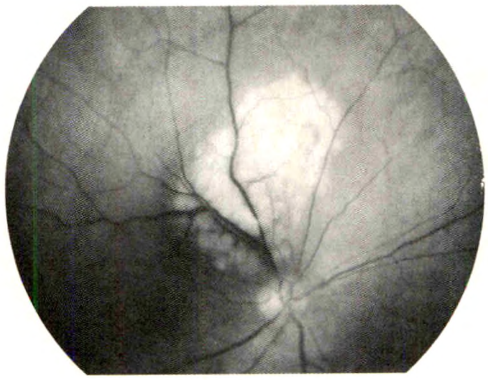


TABLE 2
PATIENTS WITH SMALL CHOROIDAL MELANOMAS NOT RECEIVING LASER PHOTOCOAGULATION

PATIENT NO., AGE (YRS), SEX	TUMOR DIMENSION (MM)		INITIAL ASSESSMENT TO FIRST NOTED GROWTH (MOS)	FINAL OUTCOME	FOLLOW-UP AFTER TREATMENT (MOS)
	INITIAL	AFTER GROWTH			
1, 65, M	4 × 4.5 × 2.7	4.5 × 4.5 × 3.4	14	Enucleation (mixed cell)	22
2, 54, M	6 × 9 × 2.5	6.5 × 9 × 3.7	9	Enucleation (mixed cell)	14
3, 20, M	6 × 6 × 2.3	6 × 7 × 3.7	4	Enucleation (mixed cell)	19
4, 64, M	6 × 7.5 × 2.4	No change	—	Observation	19
5, 71, F	6 × 6 × 2.4	No change	—	Enucleation (mixed cell)	7
6, 24, M	6 × 7.5 × 2.3	7.5 × 8 × 3.4	15	I 125 brachytherapy	24
7, 56, F	4 × 4 × 2.0	6.5 × 7.5 × 2.7	6	Enucleation (mixed cell)	15
8, 56, M	4 × 4.5 × 1.6	4.5 × 4.5 × 2.4	5	Observation	5
9, 55, F	6 × 6.5 × 2.9	7.0 × 8.5 × 3.7	26	Observation	104

Discussion

Most clinically suspected small and large choroidal melanomas accompanied by a serous macular detachment show eventual growth. Gass[3] noted growth in 63% of large tumors with serous detachments of the macula. Erie and Robertson[2] reported growth over a mean interval of two years in six of eight eyes containing small choroidal melanomas with subretinal fluid involving the macula. With longer follow-up in this original series, one additional tumor also grew (seven of eight tumors).

In this study, we reviewed the records of 22 patients with presumed small choroidal melanomas who had a serous macular detachment on initial examination. We included only melanotic tumors that, at the time of initial examination, were 4 to 10 mm in greatest base diameter and 1.5 to 3 mm in height. The eight cases reported earlier[2] were included in the review. Nineteen of the 22 eyes (86%) with small melanomas and serous detachments of the macula grew over a mean interval of less than two years.

The study by Erie and Robertson[2] and that of Gass[3] showed that minimal to moderately intense surface photocoagulation applied to focal or diffuse areas of leakage, or both, may eliminate subretinal fluid in the macula and improve visual acuity. Thirteen of the 22 tumors reviewed in the present study were treated with argon laser surface photocoagulation in a nonrandomized fashion. With one or two treatments, fluid resorption occurred in 11 of 13 eyes (85%), vision improved two or more lines in Snellen acuity in eight eyes (62%), with six eyes (46%) returning to a visual acuity of 20/25 or better. Twelve of the 13 tumors (92%) showed distinct growth over a mean interval of 23 months after initial examination. All 12 had significant growth in basal diameter (0.5 mm or more) with seven (54%) developing a collar-button growth pattern. Eleven of the 12 tumors (92%) that showed growth received further treatment. Seven eyes were enucleated, and four were treated with iodine 125 brachytherapy. Six of the enucleated specimens were mixed-cell choroidal melanomas, and one was a spindle B choroidal melanoma.

Nine of the 22 tumors were not treated with

Figure (Erie, Robertson, and Mieler). Patient 6. Top row left, Fundus shows pigmented tumor superior to fovea of right eye on initial examination. A serous detachment surrounds the tumor and extends into the fovea. Top row right, Early phase of initial angiogram shows focal areas of dye leakage. Second row left, Effect of argon laser photocoagulation that was directed to the surface of the tumor is shown. The subretinal fluid resolved within weeks of treatment. Second row right, Fundus six months after initial laser treatment shows temporal expansion of the tumor (arrows) and recurrence of the subretinal fluid. Third row left, Late phase of angiogram shows areas of focal and diffuse leakage over the surface of the tumor. Third row right, Effect of second confluent argon laser photocoagulation that was directed to the entire surface of the tumor is shown. The subretinal fluid resolved within weeks of treatment. Bottom row left, Tumor growth through Bruch's membrane in a collar-button configuration noted four months after second treatment with argon laser.

surface photocoagulation despite the presence of fluid in the macula causing a reduction in central visual acuity. The visual acuity remained unchanged or deteriorated further in all nine patients. Seven of the tumors (78%) showed growth over a mean interval of 11.3 months after initial examination. Although all seven showed enlargement in both basal diameter and in height, none had a collar-button configuration. Five eyes were enucleated, and one received iodine 125 brachytherapy. All enucleated specimens were mixed-cell choroidal melanomas.

Although photocoagulation therapy applied over the tumor surface generally results in fluid resorption and improvement in visual acuity, previous studies questioned whether such photocoagulation influenced the tumor's growth pattern.[2,4] Of the 22 eyes in this study, subsequent growth of the choroidal tumor in basal dimension and in height occurred in 19 eyes (86%). Seven of nine tumors (78%) that did not undergo surface photocoagulation grew. Twelve of 13 tumors (92%) that received surface photocoagulation grew. Seven (57%) of those tumors receiving surface photocoagulation, however, exhibited growth in a collar-button configuration, whereas such a growth pattern was not seen in the nine eyes with tumors that did not receive surface photocoagulation. In all eyes in which a collar-button configuration was observed, the base of the tumor also expanded. Because most of those tumors not receiving laser treatment also showed evidence of growth both in basal dimension and in thickness, we conclude that photocoagulation is not responsible for the tumor growth. Instead, our observations suggest that photocoagulation treatment to the surface of a growing choroidal melanoma increases the likelihood of tumor expansion through Bruch's membrane in a collar-button configuration, in spite of the laser being applied with minimal-to-moderate intensity over the tumor's surface.

Observed growth does not always indicate malignancy; small tumors that grow during observation may prove histopathologically to be benign spindle-cell tumors.[1] Growth, however, is considered by many to be a clinical indicator of possible malignancy in small melanotic choroidal tumors. In our series, all 11 enucleated eyes showed malignant cellular patterns. In ten eyes, the tumor was composed of both epithelioid cells and spindle B cells.

Whether growth through Bruch's membrane is associated with an increased incidence of metastasis is unclear. One series suggested increased mortality in patients who had choroidal melanomas with a collar-button configuration.[5] In that series, however, extension through Bruch's membrane was closely related to the tumor's largest diameter. Possibly the slightly worse prognosis associated with extension through Bruch's membrane was attributable to the greater size of the tumor.

In our series, 21 of the 22 patients are alive and free of metastasis, although the mean follow-up from the time of the initial examination was only 52 months (range, five to 120 months), and the mean follow-up from the time of treatment with brachytherapy or enucleation was 36 months (range, seven to 120 months). In one patient, death occurred after five years of follow-up, and the cause of death was unknown.

Because of our observations, we presently are not performing surface photocoagulation over small choroidal melanomas with serous macular detachments.

References

1. Gass, J. D. M.: Problems in the differential diagnosis of choroidal nevi and malignant melanomas. Trans. Am. Acad. Ophthalmol. Otolaryngol. 83:19, 1977.

2. Erie, J. C., and Robertson, D. M.: Serous detachments of the macula associated with presumed small choroidal melanomas. Am. J. Ophthalmol. 102:176, 1986.

3. Gass, J. D. M.: Observation of suspected choroidal and ciliary body melanomas for evidence of growth prior to enucleation. Ophthalmology 87:523, 1980.

4. Folk, J. C., Weingeist, T. A., Coonan, P., Blodi, C. F., Folberg, R., and Kimura, A. E.: The treatment of serous macular detachment secondary to choroidal melanomas and nevi. Ophthalmology 96:547, 1989.

5. Shammas, H. F., and Blodi, F. C.: Prognostic factors in choroidal and ciliary body melanomas. Arch. Ophthalmol. 95:63, 1977.

Age-related Macular Changes in Humans Over 90 Years Old

Lynette Feeney-Burns, Ph.D., Robert P. Burns, M.D., and Chun-Lan Gao, M.D.

The macula lutea of 23 donors aged 90 to 101 years were examined by light and electron microscopy and compared to maculas from a 49- to 68-year-old age group. The number of foveal photoreceptors and retinal pigment epithelial cells, the presence of macular pigment, and lipofuscin fluorescence were assessed. Pathologic characteristics typical of age-related macular degeneration occurred in nine of the 90- to 101-year-old group with changes ranging from early neovascularization to fully developed disciform scars, geographic atrophy, and macular holes. Several retinas had pigment epithelial and photoreceptor cell numbers equal to those of the younger group, but most showed cell loss. Thickened, debris-filled Bruch's membrane and choriocapillary atrophy, although common, were not an invariable accompaniment to old age. Clinicians should advise elderly patients that their chances of maintaining macular structure, and hopefully function, are better than 50%.

THE AGING PROCESS results in numerous changes in cells and tissues of the body, but few are as important to an elderly individual as those occurring in the 2- to 3-mm^2 area of macular retina, loss of which can profoundly affect the quality of life.

Knowledge about the histologic characteristics of the retina and the macula in elderly subjects is meager. Several studies have reported an age-related decrease in the number of foveal cones (based on histologic characteristics) or of density of cone pigments measured in vivo.[1] Few of the cited investigations, however, included eyes from subjects over 90 years of age. Likewise, studies of pigment epithelium have seldom included individuals of this age.

We studied 35 macular specimens from 23 individuals 90 to 101 years of age and compared them to maculas from a group of middle-aged individuals (49 to 68 years old) for number of pigment epithelial cells and photoreceptors and other morphologic features. By examining specimens from elderly subjects, we attempted to define those changes that accompany aging without necessarily initiating pathologic processes.

Material and Methods

Donor age, sex, interval between death and tissue fixation, and observations made during dissection are listed in Table 1. All subjects were white. Whole eyes, or that part remaining after the cornea was removed, were fixed by immersion in 2% glutaraldehyde, 1% paraformaldehyde in cacodylate buffer containing potassium and calcium chloride, and sucrose.[2] Fixation varied from six hours to several weeks. A 5-mm^2 block of macular tissue was excised by using a dissecting microscope. The block was then bisected vertically through the foveola; this caused minor cracking at the inner retinal surface, which is an easily identified artifact in the first few sections from the block face. Tissue was dehydrated and embedded in epoxy resin. When pairs of eyes were received unfixed, one eye was fixed for histologic examination as above and the fellow eye was dissected for additional studies as follows: the posterior neurosensory retina was mounted on a slide to examine the distribution of luteal pigment, and the macular region of the retinal pigment epi-

Accepted for publication Dec. 14, 1989.

From the Mason Institute of Ophthalmology, University of Missouri-Columbia, Columbia, Missouri. This study was supported in part by a research grant from the National Eye Institute (EY 03274) and an unrestricted grant from Research to Prevent Blindness, Inc. Dr. Feeney-Burns is a Research to Prevent Blindness Senior Scientific Investigator.

Reprint requests to Lynette Feeney-Burns, Ph.D., Mason Institute of Ophthalmology, University of Missouri-Columbia, Columbia, MO 65212.

thelium remaining in the posterior eye cup was either scraped off, mounted on a slide and cover slipped, or frozen for subsequent sectioning. Both of the pigment epithelial preparations were then examined by fluorescence microscopy (365 nm excitation: >449 nm emission) for the presence of lipofuscin granules.

Semithin (0.5 μm) serial step (8.5-μm intervals) sections were cut from ten of the eyes so that 20 to 50 sections were examined to assess variability. For the other specimens not amenable to serial sectioning, two to five sections were studied. All sections were stained with toluidine blue O for light microscopy. Many specimens were not used for cell counts because edema or distortion of the foveal retina had caused misalignment of tissue layers or other orientation problems.

Selected areas of the specimens were trimmed, thin sectioned, and stained with uranyl and lead salts for transmission electron microscopy. Specimens were viewed and photographed in an electron microscope.

Sections through the foveola of blocks approximately 3 mm wide (Fig. 1) were examined with a light microscope equipped with a 40× oil immersion planapochromatic objective lens, numerical aperture 1.0, and an eyepiece measuring grid. Any pigment epithelial cell nucleus or fraction thereof visible in sections was counted along the entire length of the section and expressed as nuclei per millimeter. Cells and fractions thereof were likewise estimated based on such features as nuclear spacing, doming, and pigment clustering (Fig. 2). Pigment epithelial nuclei and cells in the central 600 μm were recorded separately. All photoreceptor nuclei in the 600-μm area of the foveal depression (Fig. 1) were counted. Measurements of photoreceptor outer segment length by light microscopy were made only on specimens that showed no sag or collapse of the neural retina onto the pigment epithelium.

Numerical data were analyzed statistically, and groups were compared using the two sample t-test.

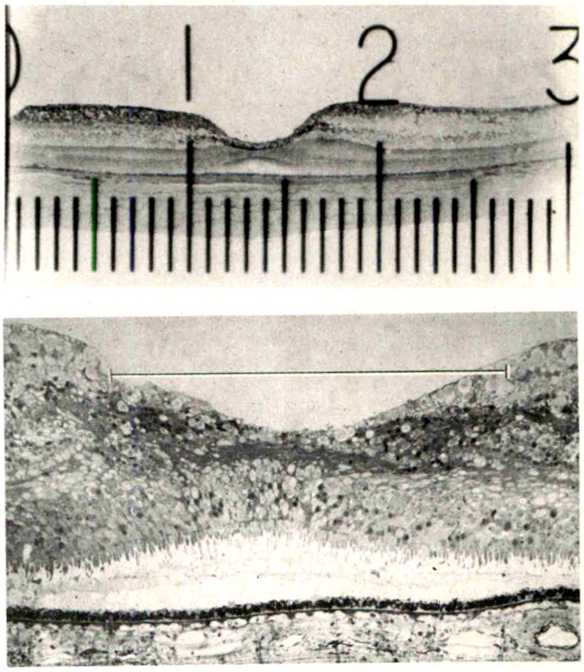


Fig. 1 (Feeney-Burns, Burns, and Gao). Top, Macular section from a 101-year-old donor eye photographed through a dissecting microscope with an overlying millimeter scale. Foveal detachment is typical in these donor specimens. Bottom, Microscopic appearance of above donor fovea. Neuronal edema, presumably post mortem, is apparent; photoreceptor nuclei within 600-μm width were counted. Pigment epithelium appears normal, and there are no drusen (micrographic montage minimizes the detachment space [× 135]).

Results

Abnormalities of macular specimens from 90- to 101-year-old donors ranged from a small focal degeneration of the foveal retina with adhesion to the pigment epithelium, to larger areas of photoreceptor loss without associated scarring or neovascularization, to subpigment epithelial neovascularization, to various degrees of subretinal neovascularization, to several cases of disciform macular scarring, which is the end stage of age-related macular degeneration. In several specimens with disciform scars, the pigment epithelium was discernible but in a greatly altered form; it was often amelanotic and flat, the sparse cytoplasm being stretched to make focal contacts with adjoining cells. A layer of material resembling the basal linear deposit[3] was identified beneath these altered pigment epithelial cells. The histopathologic characteristics of these specimens did not differ in any recognizable way from changes accompanying age-related macular degeneration described in the literature.[3-5]

Of the 33 sectioned maculas from persons 90 to 101 years old, 13 specimens were free of retinal pathologic changes that characterize

TABLE 1
DONOR INFORMATION AND CHARACTERISTICS OF SPECIMENS

DONOR	ELECTRON MICROSCOPY NO.	AGE (YRS)	SEX	TIME BETWEEN DEATH AND SPECIMEN FIXATION (HRS)	CAUSE OF DEATH	OCULAR HISTORY	TISSUE STUDY* OR RETINAL HISTOLOGIC CHARACTERISTICS†	DRUSEN‡
					Older Group (35 Specimens)			
1	1213	90	F	13	Leukemia	No disease[§]	Macular pigment	NA
	1214	—	—	—	—	—	Normal	Yes
2	1230	90	M	3.5	Pneumonia	Unoperated on senile cataract[‖]	Normal	Yes
	1231	—	—	—	—	—	Normal	Yes
3	1224	90	M	9.5	Cancer	Legally blind[‖]	Fovea detached, normal	No
	1225	—	—	—	—	—	Fovea detached, normal	No
4	089	91	F	10	Unknown	No disease[¶]	Subretinal neovascularization	Presumed
5	653	92	F	2.5	Heart failure	Legally blind[‖]	Age-related macular degeneration, disciform scar	Presumed
6	027	92	F	?	Unknown	No disease[¶]	Age-related macular degeneration, scar	Presumed
7	483	92	F	3.0	Cancer	No disease**	Subpigment epithelial neovascularization, small scar, macular pigment	Yes ND
8	723	92	F	8.5	Heart failure	No disease[¶]	Fovea detached, normal	No
	724	—	—	—	—	—	Fovea detached, normal	No
9	974	92	F	9.5	Stroke	Corneal transplant, phakia	Hole, cystoid edema	Presumed
	975	—	—	—	—	Aphakia	Subpigment epithelial neovascularization, thin fovea	Yes
10	1090	92	M	12	Stroke	Aphakia	Fovea detached, normal	Yes
	1091	—	—	—	—	Aphakia	Retina detached, normal	Yes
11	1177	92	F	3.5	Cancer	Aphakia, could read[‖]	Frozen section	ND
	1178	—	—	—	—	—	Macular pigment	ND
12	1198	93	F	39	Renal failure	No disease††	Fovea detached, thin	No
13	1058	93	F	?	Unknown	No disease[¶]	Fovea detached, thin	Yes
	1059	—	—	—	—	—	Fovea detached, thin	Yes
14	1148	93	F	?	Cancer	No disease††	Fovea detached, thin	No
	1149	—	—	—	—	—	Fovea detached, thin	Yes
15	732	95	M	?	Unknown	No disease[¶]	Foveal scar, no subretinal neovascularization	Yes
	733	—	—	—	—	—	Scar	Presumed
16	1223	95	M	6	Heart attack	No disease**	Atrophic, age-related macular degeneration, hole, macular pigment	ND

Table continued on following page.

age-related macular degeneration (Table 2). Of these, seven specimens were morphologically normal, and six had detached but near normal retinal morphologic characteristics. An additional group of seven specimens with detached retinas and thinned or edematous neural retina but otherwise lacking disease was included with the above normal specimens for

TABLE 1 *(Continued)*
DONOR INFORMATION AND CHARACTERISTICS OF SPECIMENS

DONOR	ELECTRON MICROSCOPY NO.	AGE (YRS)	SEX	TIME BETWEEN DEATH AND SPECIMEN FIXATION (HRS)	CAUSE OF DEATH	OCULAR HISTORY	TISSUE STUDY* OR RETINAL HISTOLOGIC CHARACTERISTICS†	DRUSEN‡
				Older Group (35 Specimens)				
17	1229	95	F	14	Heart attack	Intraocular lens, no disease††	Normal	Yes
18	524	96	F	9	Anemia	No disease¶	Age-related macular degeneration, disciform scar	Presumed
19	668	96	F	?	Heart failure	No disease¶	Fovea detached, thin	Yes
20	711	97	F	?	Unknown	No disease¶	Age-related macular degeneration, disciform scar	Presumed
21	1219	97	F	11	Heart failure	No disease¶	Normal	No
	1220	—	—	—	—	—	Normal	Yes
22	1087	98	F	6	Heart failure	No disease**	Age-related macular degeneration, scar	Presumed
23	1167	101	F	2	Heart failure	Corneal transplant	Cystoid edema	No
	1168	—	—	—	—	Aphakia, could read‖	Normal	No
				Middle-Aged Group (10 Specimens)				
1	858	49	M	1.5	Cancer	No disease††	Normal	No
	859	—	—	—	—	—	Normal	No
2	561	52	F	12	Heart attack	No disease**	Normal	No
3	550	53	M	6	Heart attack	No disease§	Detached fovea	No
4	923	55	F	18	Emphysema	Pseudophakia	Detached fovea	No
5	588	56	F	5	Cancer	No disease††	Detached fovea	No
6	900	63	M	4	Postoperative sepsis	Macular drusen‖	Detached fovea	Yes
7	1287	66	M	24	Alzheimer's disease	No disease††	Detached fovea	No
8	973	68	M	3	Cancer	No disease††	Detached fovea	No
9	701	68	M	2	Cancer	No disease††	Normal	No

*Tissue study: for macular pigment, neural retina was examined in flat preparation for the presence of yellow macular pigment. For frozen sections, 6-μm thick sections were examined with ultraviolet light for amount of autofluorescence in the pigment epithelium.

†Retinal histologic characteristics: 0.5-μm epoxy resin sections of tissue were examined at low magnification.

‡NA indicates not available; No, none found in semithin sections; Yes, at least one found; Presumed, presumed to have been present or buried in scar; ND, no epoxy sections prepared.

§Nurse/technician stated that there was no ocular disease.

‖Data from family or physician.

¶Notation on eye bank form.

**Chart examined by eye bank technician; no ocular history found.

††Primary physician stated, "no ocular disease."

analytic comparisons. All but one person in this group with relatively normal macular morphologic characteristics had marked thickening and alterations of Bruch's membrane (Figs. 2 and 3). Additionally, drusen were found in six of the 20 specimens with normal retinas (Table 2) and in all of those with pathologic retinal changes.

The results of macular cell counts of eyes from donors over 90 years of age compared to eyes from middle-aged donors are shown in Table 3. The average number of pigment epithelial cell nuclei per millimeter of sectioned macula from the elderly group is significantly smaller than that of the middle-aged group. The estimated number of pigment epithelial cells per millimeter is also significantly less in

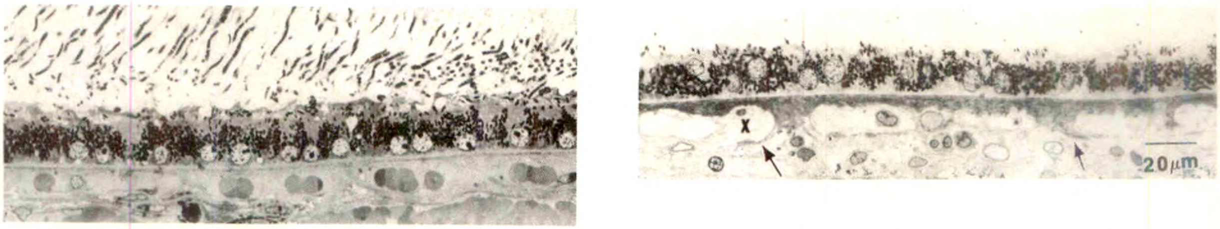


Fig. 2 (Feeney-Burns, Burns, and Gao). Comparison of retinal pigment epithelium, Bruch's membrane, and choriocapillaris of a 51-year-old donor (left) and a 101-year-old donor (right). More nuclei and pigment epithelial cells are apparent in the younger eye (13 nuclei and 22 cells in the younger specimen vs ten nuclei and 19 cells in the older specimen). Cells of the older eye are slightly shorter. Note in the older specimen the thicker Bruch's membrane with its debris trailing outward into the choroid (arrow), and the debris-free cuff that surrounds the capillaries (x) (×550).

the older age group. The cell/nuclear ratio, however, is only marginally less and not statistically different. Using these data, the calculated average nuclear spacing and cell widths of macular pigment epithelial cells are much greater in the old than in the middle-aged group. Measurements of cell height disclosed that cells of the fovea and parafovea of older eyes were slightly shorter than those of the middle-aged group (Table 3).

Foveal data are shown in Table 4. For this analysis, two specimens that had zero values because of small (less than 500 μm) scars were removed from the older group. Additionally, a specimen from a donor with Alzheimer's disease was removed from the middle-aged group because the aim of this analysis was to compare numbers of cells in tissue from old and middle-aged donors lacking recognizable or diagnosed disease. The number of pigment epithelial cells in the central fovea of the old group was significantly smaller compared to the middle-aged group. Photoreceptors also were significantly fewer in the older group. The ratio of retinal pigment epithelial cells to photoreceptors, however, remained approximately the same for both groups, suggesting a balanced cell deletion in the two layers.

Individual donors' pigment epithelial data as a function of age are plotted in Figure 4. The middle-aged group showed less variability in cell/nuclear ratios than the older group. Greater cell size (highlighted by the space between the C and N points, representing pigment epithelial cells and their nuclei, respectively, on the plot) is apparent in many more of the specimens from the 90- to 101-year-old group.

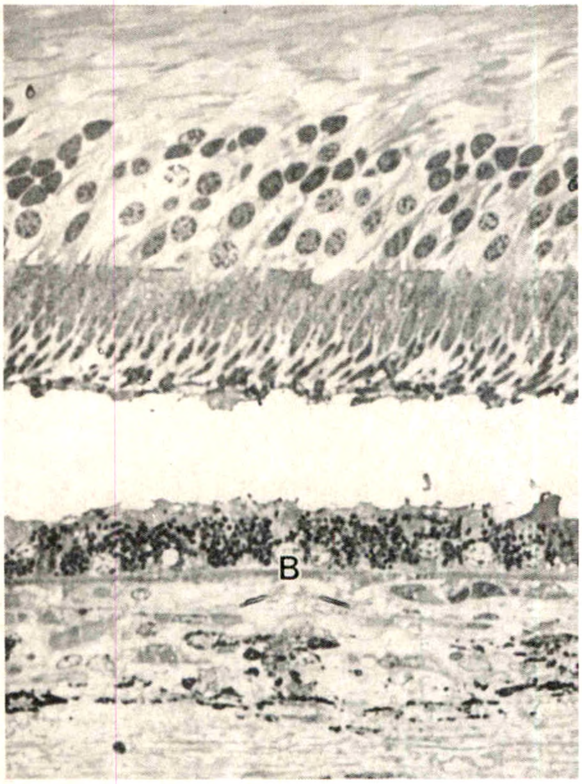
Numbers of pigment epithelial cells and photoreceptors in a 600-nm wide zone of the fovea from specimens from the 90- to 101-year-old group and middle-aged controls are shown in Figure 5. This plot highlights deviations from the normal ratio (approximately 1:6) of the two cell types found in the middle-aged group (Table 4). The 49- to 68-year-old age group showed fairly consistent cell counts, although the 66-year-old donor with Alzheimer's disease had fewer foveal photoreceptors than the others. Much variation was found in the older group. In many cases, photoreceptor cell losses exceeded retinal pigment epithelium losses (specimens 13, 14, 20, 21, 23; Fig. 5), which suggests that

TABLE 2

HISTOLOGIC FINDINGS* IN SPECIMENS FROM DONORS OVER 90 YEARS OF AGE

CONDITION	SPECIMENS (N = 33)	INDIVIDUALS (N = 23)	DRUSEN† (NO. OF SPECIMENS)
Normal	(13, 39%)	—	3
No abnormality	7	—	—
Detached normal retina	6	—	—
Probably normal	(7, 21%)	—	3
Detached, thinned retina	6	—	—
Edematous retina	1	—	—
	—	14 (61%)	—
Age-related macular degeneration	(13, 39%)	—	—
Degeneration of foveal retina, focal to extensive	2	—	2
Early subretinal neovascularization	1	—	1
Subpigment epithelial neovascularization	2	—	2
Disciform scar	6	—	‡
Hole in neural retina	2	—	‡
	—	9 (39%)	—

*Determined by low-magnification light microscopy.
†Determined by high-magnification light microscopy.
‡Obscured by scarring, presumed present earlier.



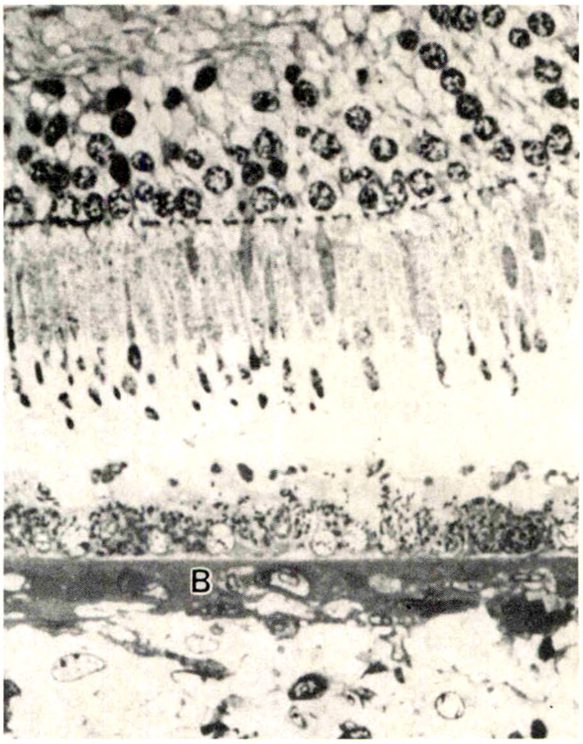


Fig. 3 (Feeney-Burns, Burns, and Gao). Two different 90-year-old specimens show a difference in the thickness of Bruch's membrane (B) (left, donor 2; right, donor 3). Both specimens had nearly normal numbers of pigment epithelial cells and photoreceptors (see data plotted in Figure 5) (×550).

photoreceptor loss is not invariably linked to pigment epithelial cell loss. In other cases, both cell types appeared to have declined (or, conversely, remained healthy) together.

The length of the outer segments in very old eyes is of interest because it may provide insight into possible age-related changes in the synthetic or the degradative processes in outer

TABLE 3

MACULAR PIGMENT EPITHELIUM OF SPECIMENS FROM MIDDLE-AGED AND NONDISEASED ELDERLY DONORS*

	SPECIMENS FROM DONORS 49–68 YEARS OLD (N = 8)		SPECIMENS FROM DONORS OVER 90 YEARS OLD (N = 14)		
	MEAN	RANGE	MEAN	RANGE	P VALUE†
Retinal pigment epithelium nuclei/mm	44.2 ± 4.8	(39–53)	30.0 ± 10.7	(9–42)	.0006
Retinal pigment epithelium cell/mm‡	85.1 ± 6.0	(78–95)	64.5 ± 3.4	(16–100)	.0069
Cell/nucleus ratio	1.9 ± 0.15	(1.7–2.2)	2.2 ± 0.38	(1.8–3.1)	.3390
Nuclear spacing (μm)	23.1 ± 2.2	—	41.5 ± 24.7		
Cell width (μm)	11.7 ± 0.7	—	18.7 ± 12.0	—	—
Cell height (μm; N=14)					
Fovea	18.1 ± 0.6§	—	16.98 ± 1.9	—	—
Parafovea	16.6 ± 1.9	—	14.56 ± 2.8	—	—

*Data from pairs of eyes randomized for analysis.

†Two-sample *t*-test with adjustment for unequal variances.

‡Estimate based on morphologic features.

§By contrast, macular pigment epithelium in formalin-fixed paraffin-embedded sections measure 10-11 μm tall.[21]

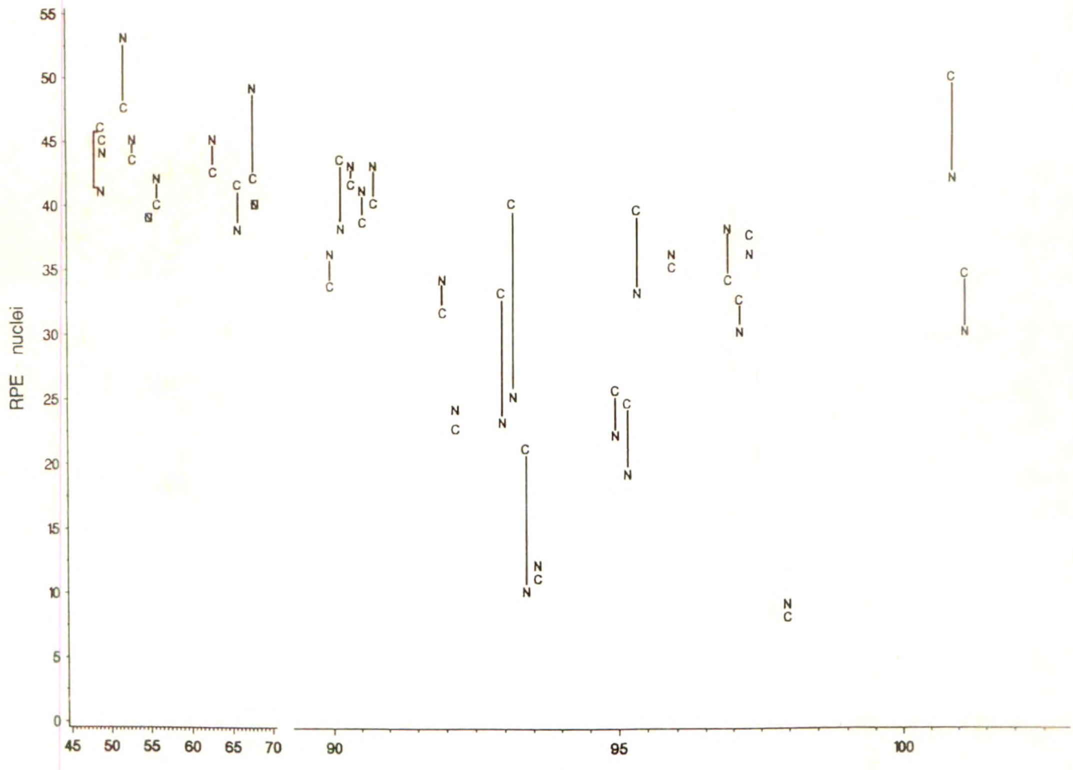


Fig. 4 (Feeney-Burns, Burns, and Gao). Plot of pigment epithelial cells (C) and their nuclei (N) vs age. (To obtain cell numbers, multiply nuclear values by two.) The older group shows more variation than the younger group, reflecting greater cellular pleomorphism.

segment disk turnover. In the middle-aged group, inner and outer segments measured 60 μm. In a specimen from a 97-year-old donor (specimen 21, Fig. 6) where no sagging or kinking of the segments existed, inner plus outer segments measured 60 μm at the fovea. Several other specimens from the 90- to 101-year-old group measured 60 μm. Thus no definitive evidence of age-related abnormalities in outer segment length was found in these macular specimens.

In addition to the quantitative data on the

TABLE 4

PHOTORECEPTORS AND PIGMENT EPITHELIAL CELLS IN THE 600-μM HUMAN FOVEA*

	SPECIMENS FROM DONORS 49–68 YEARS OLD (N = 8*†)		SPECIMENS FROM DONORS OVER 90 YEARS OLD (N = 14)		
	MEAN	RANGE	MEAN	RANGE	P VALUE‡
Retinal pigment epithelium cells§	52.2 ± 4.0	(49–59)	37.4 ± 16.5	(0–55)	.0021
Photoreceptors	307.3 ± 19.9	(282–339)	195 ± 12.3	(0–395)	.0222
Ratio‖	5.8 ± 0.5	(5–6.7)	5.3 ± 1.7	(2.7–8.2)¶	.3144

*Data from pairs of eyes randomized for analysis.

†Alzheimer's disease donor not included.

‡Two-sample *t*-test with adjustment for unequal variances.

§Estimate based on morphologic features.

‖Total photoreceptors divided by total pigment epithelial cells in 608-μm width.

¶Two zero values deleted; N = 12.

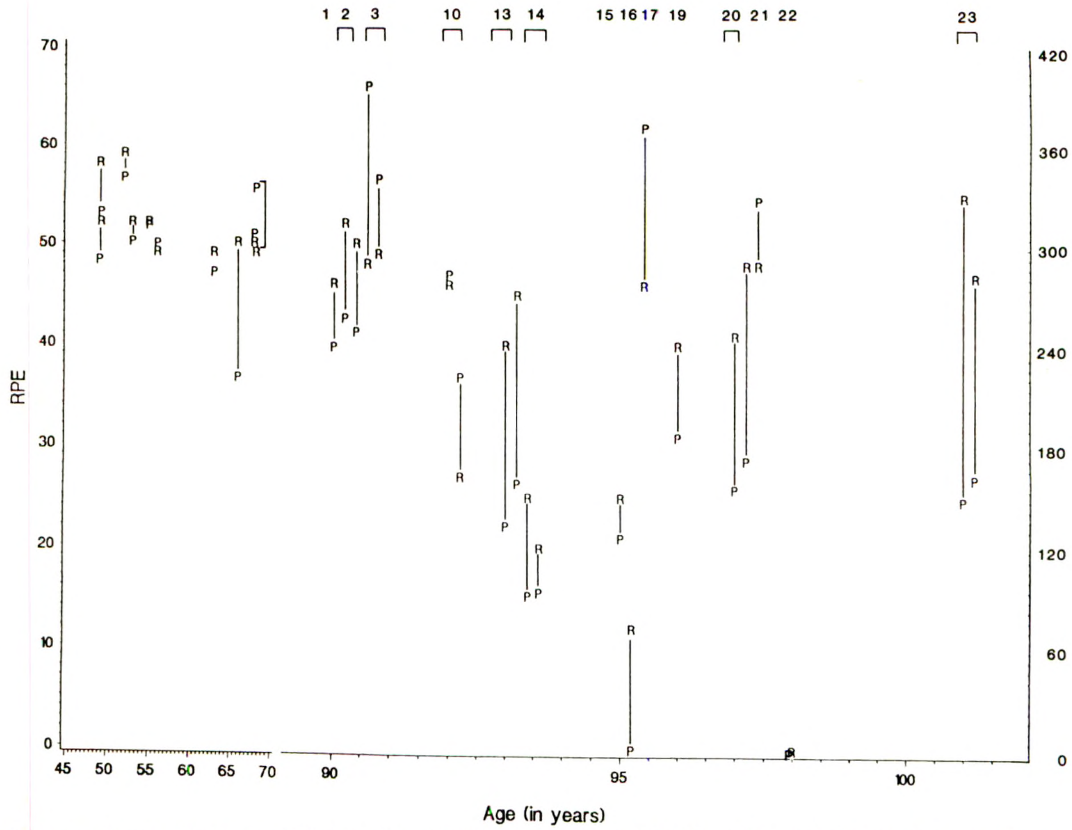


Fig. 5 (Feeney-Burns, Burns, and Gao). Plot of retinal pigment epithelium (R) and photoreceptors (P) in 0.6 mm of sectioned foveas of specimens in the 49- to 68-year-old and 90- to 101-year-old age groups. Donor numbers are given at the top. Only minor deviation from a 6:1 P:R ratio is seen in the younger group whereas the older eyes show great variation. In the older group, two thirds of the specimens have R values higher than P values; in only five cases (donors 3, 10, 17, and 22) are P values significantly higher than R values.

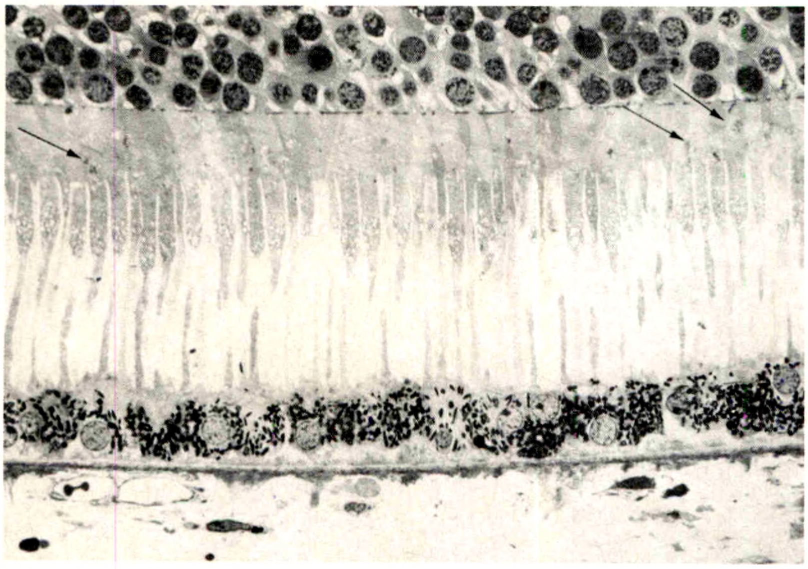


Fig. 6 (Feeney-Burns, Burns, and Gao). Photomicrograph of specimen from a 97-year-old donor (donor 21) shows parafoveal photoreceptors and pigment epithelium and normal inner and outer segment length. Arrows indicate cone lipofuscin granules (× 550).

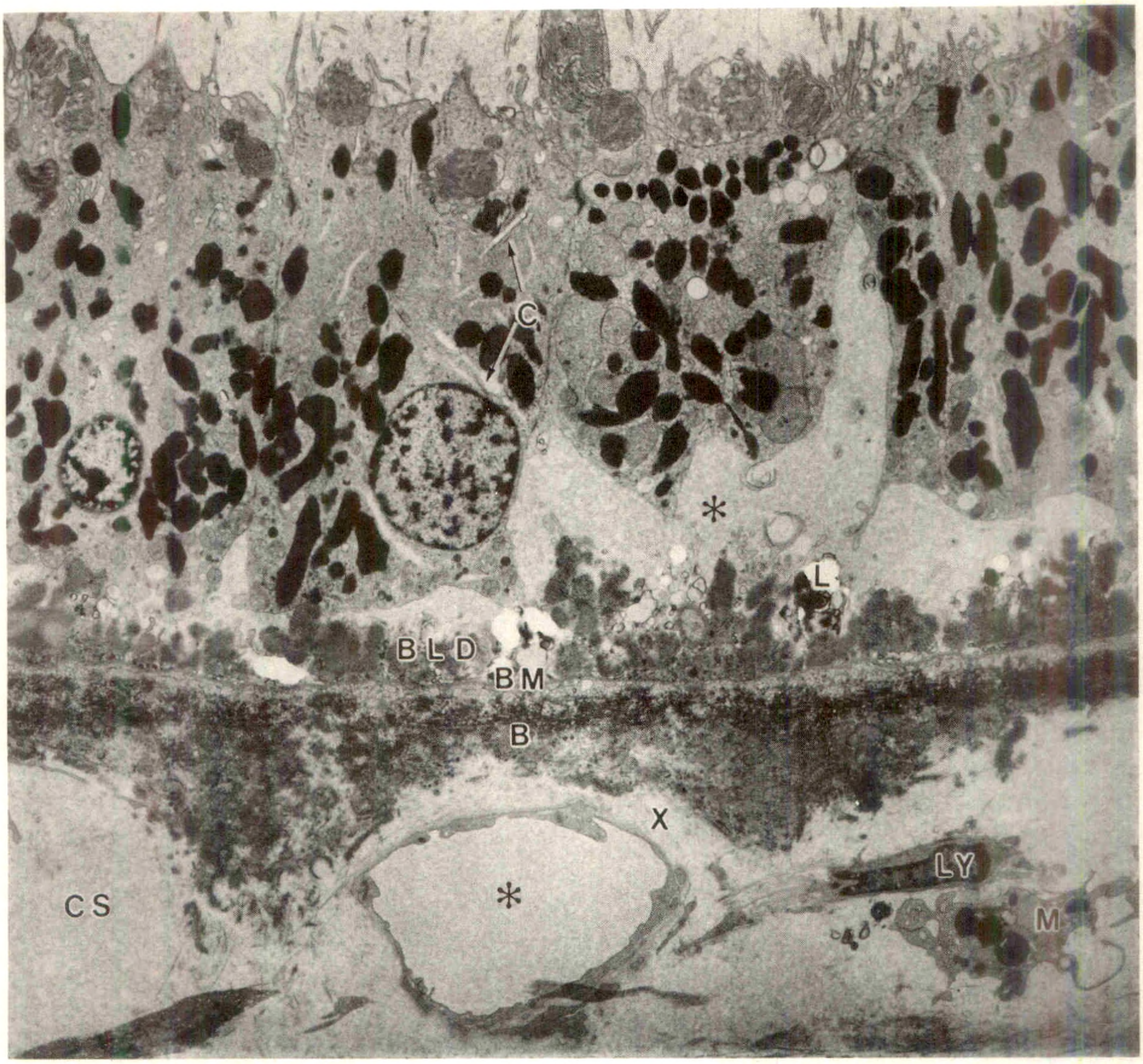


Fig. 7 (Feeney-Burns, Burns, and Gao). Electron micrograph of pigment epithelium and the inner choroid of 97-year-old donor. Outer segments and phagosomes are piled up at the apical pole of the epithelial cell. A continuous basal linear deposit (BLD) containing lipid (L) lines the inner surface of (and perhaps partially separates or detaches the epithelium from its normal attachment to) the basement membrane (BM). Bruch's membrane (B) is filled with debris that extends into the choroid, but note debris-free cuff at X and in Figure 2. Exudate, which resembles the contents of the capillary lumen (asterisks), further elevates some cells. Two cells in the choroidal stroma resemble a lymphocyte (LY) and a macrophage (M). C indicates clefts in the Golgi region lined by dense membrane; CS, capillary space ("ghost") unpenetrated by Bruch's membrane debris (× 4,600).

individual specimens, qualitative data were collected, including features of the pigment epithelium and choroid that are thought to be involved in early steps in the evolution of age-related macular degeneration, that is, the basal linear deposit, drusen, Bruch's membrane changes, and choriocapillary and choroidal atrophy. The middle-aged group contained only one specimen with a continuous basal linear deposit, and two specimens with an intermittent basal linear deposit; two of these also had subclinical drusen (shedding sites),[6] and both specimens were from patients between 60 and 70 years old. In the older group, all but three specimens had the typical, banded, basal linear deposit (Fig. 7); the three exceptions were both eyes of a 90-year-old donor (whose retina had normal numbers of cells; donor 3, plotted in

Figure 5) and one eye of the 101-year-old donor (the eye with cystoid macular edema; donor 23, Table 1).

Drusen were found in 11 of the older specimens, but because only a small fraction of the macular tissue was sampled (about 3 mm wide, <0.5 mm deep at the foveal center), there were undoubtedly many more specimens with drusen. Discrete domed (hard)[7] drusen were present in both maculas of a donor (donor 10, Fig. 5) with normal retinas. Drusen with shallow undulating profiles containing sparsely staining membrane-like material[7] (also known as soft, confluent, or possibly exudative drusen[5]) occurred more often in specimens that showed retinal disease or photoreceptor cell loss or both (donors 15, 16, 22; Fig. 5). A basal linear deposit was invariably present internal to the basement membrane of the pigment epithelium in all cases of soft drusen, as previously noted by Sarks and associates.[7]

Atrophy of the choriocapillaris and the choroid were also assessed in the specimens for which morphometric data were tabulated. Patchy atrophy (at least one occluded capillary per millimeter of section) was found in only one specimen (Alzheimer's disease) from the middle-aged group. In the older group, most of the eyes had some degree of choriocapillary atrophy. Eyes from donors 3, 19, 22, and 23, aged 90, 96, 98, and 101 years old, respectively, were particularly atrophic (Figs. 5 and 7), but whereas the eye from the 98-year-old donor had lost all foveal pigment epithelium and photoreceptors, the eyes from the 90-, 96-, and 101-year-old donors had normal pigment epithelium and only slightly reduced numbers of photoreceptors (Fig. 5); this indicates that capillary atrophy is not necessarily lethal to retinal cells. In the specimen from the 101-year-old, however, some vessels deeper in the choroid had fenestrated endothelium (Fig. 8), which suggests that

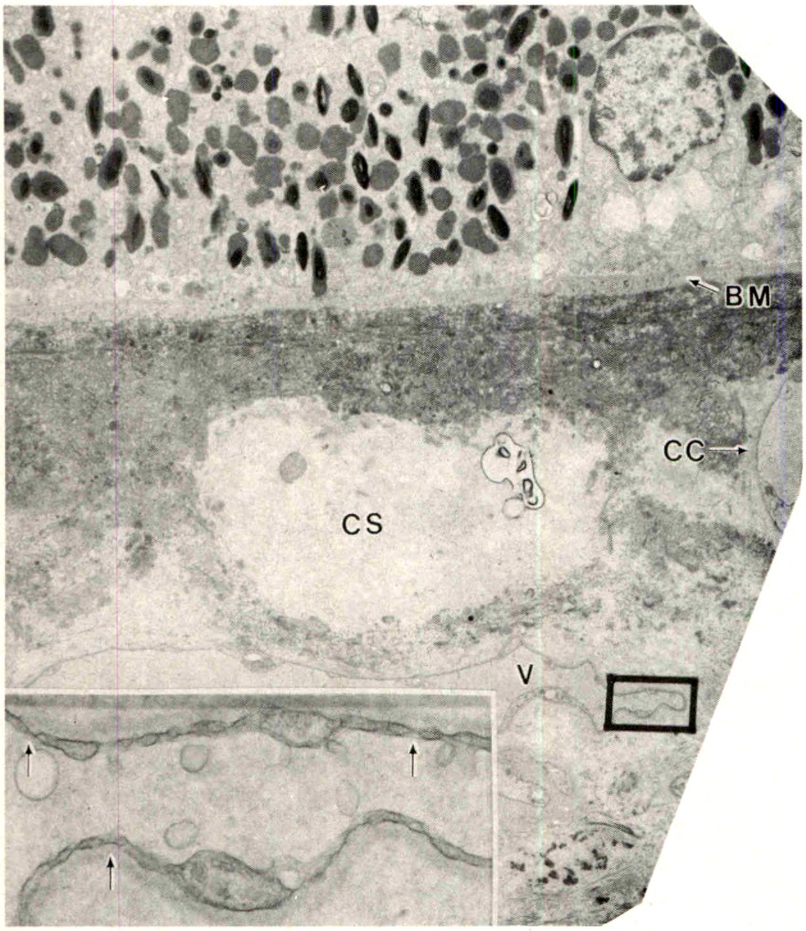


Fig. 8 (Feeney-Burns, Burns, and Gao). Pigment epithelium and inner choroid of 101-year-old donor. Note abundance of lipofuscin granules in the pigment epithelium and the well-formed basement membrane, which is unlined by basal linear deposit. CC indicates choriocapillaris; CS, space formerly occupied by a capillary; V, vessel with fenestrated endothelium; BM, basement membrane (× 3,800). Inset, Enlargement shows fenestrae typical of normal choriocapillaris (arrows) (× 24,000).

although the original capillaries had atrophied, more remote vessels had modified their structure to, perhaps, normalize the metabolic support necessary to maintain the retinal cells in these areas.

Thickness measurements could not reliably assess choroidal atrophy because of the variable blood content of the uvea. Most of the younger choroids measured 120 to 180 μm in width, with two specimens in the 90- to 100-μm range. Choroids thinner than 90 μm were considered atrophic and were found in six of the 20 nondiseased specimens from donors over 90 years of age (Fig. 5). Otherwise, despite evidence of tissue changes, choroidal thickness was not greatly altered in most of the specimens from donors over 90 years old.

Additionally, an attempt to quantify possible immunocompetent cells[8] of the inner choroid was abandoned because the terminal disease of the donor (leukemia, sepsis, and some cancers) affected the cell content of the choroidal stroma. Although there seemed to be more of these cells in the specimens from elderly donors than in the specimens from middle-aged donors, light microscopy is not adequate for determining the types and numbers of immunocytes.

Electron microscopy disclosed that the pigment epithelium of eyes from donors over 90 years old virtually lacked unadulterated melanin granules, that is, all melanin granules were encased in other material thereby creating melanolipofuscin and melanolysosomes as reported in previous studies on aging.[2] Accumulation of outer segment material at the apical surface, both inside and outside the epithelial cell of the specimen shown in Figure 7 and other specimens, suggests some impairment of phagocytic activity; alternatively, it may be a light cycle or shedding phenomenon occurring at the time of death. In the cytoplasm, lucent clefts lined by dense limiting membranes, possibly belonging to the Golgi apparatus, were noted in several well-preserved specimens (Fig. 7) and may be a result of aging. The basal surface of the pigment epithelium showed loss of basal infoldings and variable degrees of detachment from the basement membrane, apparently because of the presence of the basal linear deposit and lipoidal material (Fig. 7). Exudate beneath and between pigment epithelial cells possibly constitutes a small exudative detachment, but postmortem artifacts are difficult to rule out in such instances.

The ultrastructure of Bruch's membrane in all but one (Fig. 3) of the 90- to 101-year-old donor eyes resembled that of other eyes from old patients described in the literature. The amount of collagen in the intercapillary tissue may be somewhat greater than that seen in younger eyes, however. A cuff of finely fibrillar matrix that is not penetrated by Bruch's membrane debris (Figs. 2 and 7) typically surrounds the few remaining capillaries whose lumens are abnormally narrow. The 90-year-old specimen that lacked debris-thickened Bruch's membrane (Fig. 3) had senile cataracts that had not been operated on (Table 1).

All specimens from donors aged 90 to 99 years examined qualitatively in frozen sections by fluorescence microscopy using the standard conditions for identification of lipofuscin fluorescence disclosed typical brilliant orange-yellow fluorescent granules engorging the pigment epithelium. Fluorescent granules were not found in small drusen or at shedding sites within the inner collagenous zone of Bruch's membrane. We did not examine specimens with large drusen or with age-related macular degeneration using this technique.

Of the four retinas (donor ages 90, 92, 95, and 95 years) that were examined as flat preparations, all had yellow macular pigment, including the specimen with the apparent full thickness macular hole. In this specimen, the pigment was distributed in discontinuous blotches around the hole.

Other features of the aging neural retina found in our sample of eyes that have been reported previously[9] include displaced nuclei, particularly from the outer nuclear layer into the inner segments[10,11]; convoluted or telescoped outer segments[12]; and age pigment (refractile bodies, lipofuscin granules) in the inner segment of cones.[13,14]

Discussion

The degree to which aging over 90 years results in deterioration of the central pigment epithelium and photoreceptors has not been examined systematically. In this study, we found that most specimens had at least five tissue changes that appeared to be age-related and were not accompanied by the pathologic changes identified with age-related macular degeneration (such as subpigment epithelial or subretinal neovascularization and atrophy of

the pigment epithelium). These changes included accumulation of lipofuscin granules in the retinal pigment epithelium; loss of foveal photoreceptors; loss of pigment epithelial cells; thickening of Bruch's membrane by heterogeneous debris; and loss of choriocapillaris. None of these changes would be identifiable clinically by the ophthalmoscope, slit lamp, or fluorescein angiography. Interestingly, only lipofuscin accumulation in the pigment epithelium invariably occurred in the specimens from donors over 90 years old.

Cell counts showed that some individuals over 90 years old have as many or more photoreceptors as people nearly half their age. Specimens with a high number of photoreceptors invariably had a continuous layer of pigment epithelium, attesting to the known dependence of photoreceptors on pigment epithelium for metabolic and structural support. Incidences of photoreceptor loss without pigment epithelial cell loss were also found, however, which indicates that reduction in photoreceptors is not invariably linked to previous loss of pigment epithelium, as has been suggested.[15,16]

Early studies showed the number of pigment epithelial cells in the posterior pole[17] and the macula[18] to remain virtually constant after adulthood (based on six specimens from donors aged 30 to 96 years and six specimens from donors aged 20 to 74 years, respectively). In a recent quantitative study,[19] a significant decline was reported in numbers of pigment epithelial cell nuclei in the macula and paramacula of human specimens from donors aged up to 88 years. The disparity in the findings is most likely related to ages of subjects in the sample pools, counting methods, specimen size (the specimens described by Dorey and associates[19] encompassed paraffin sections only 90 μm long), and variability of human samples, a feature apparent when statistical data are examined. Although we found fewer pigment epithelial cells in our specimens from donors 90 to 101 years old, unlike Dorey and associates,[19] we did not find a significant change in the ratio of photoreceptors to pigment epithelial cells when comparing our middle-aged and elderly groups, thus we cannot conclude as they did that aged macular pigment epithelium is burdened by excessive numbers of outer segments to be phagocytosed.

We found the macular pigment epithelial cells to be shorter and wider rather than taller[19-21] in specimens from patients 90 to 101 years old; in this respect, the macular pigment epithelium resembles corneal endothelium, which flattens and spreads during aging. Flattening and reduced numbers of pigment epithelial cells were found also in monkeys that had developed macular pigmentary mottling and hyperfluorescence in fluorescein angiograms after being fed a semipurified diet deficient in xanthophylls for a decade.[22] These changes may contribute to pigment epithelial atrophy, which is a major component of age-related macular degeneration.

Variability of biologic specimens increases with age.[23,24] Distinguishing between the contribution of age-dependent variables and disease is a challenge when trying to assess the impact of age changes on a tissue. Weale[24] emphasized that senescent changes in the retinal pigment epithelium, Bruch's membrane, and the choriocapillaris are observed even in the absence of pathologic complications. This study confirms this observation for specimens from donors over 90 years of age. Indeed, as noted by Sarks,[3] changes in Bruch's membrane are an excellent predictor of the general health of the macula. In our study, the thickness of Bruch's membrane varied greatly among eyes from donors 90 to 101 years of age, with one 90-year-old specimen resembling an eye from a 30-year-old donor histologically (Fig. 3). This eye had bilateral unoperated on senile cataracts (Table 1), so for several years the macula was not subjected to focused light; whether this contributed to the atypical, debris-free Bruch's membrane requires further study.

Generally, thickening of Bruch's membrane appears to be a continual process, although some of the accumulated debris may be removed or undergo remodeling after it spreads into the choroid by means of the intercapillary connective tissue. It has been stated that this debris is removed by the vascular system,[4] but we are not aware of evidence (such as micrographs showing debris in transit) to support this interpretation. Removal of the debris by macrophages, at least in the first five to six decades of life, does not seem likely, because such cells are seldom seen in the intercapillary tissue until later decades,[8] when perhaps debris has spread to the external surface of the choriocapillaris.

Because comparison of maculas from the middle-aged and elderly groups in this study

showed a significant loss of both pigment epithelial and photoreceptor cells with age, we looked for manifestations of the disposal process. One likely site for pigment epithelial cell loss is on top of drusen where a cell first becomes depigmented (by jettisoning a package of pigment-laden cytoplasm into the interphotoreceptor space), and then becomes totally detached from Bruch's membrane (by the action of adjoining epithelial cells that insinuate their processes under the cell severing its connections to the basement membrane).[6] The fate of these fragments and cells appears to be the same as for outer segments—phagocytosis and disposal by nearby epithelial cells. Photoreceptor nuclei that are displaced into the inner segment[10,11] have been postulated to signify a stage in the disposal process, although their observed incidence greatly exceeds actual cell losses.[19] Definitive evidence of subsequent degradation, such as nucleolysis or dispersal in the interphotoreceptor space, could not be documented in this or other[11] studies. Pyknotic remnants were not found nor were macrophages seen to account for the disappearance of cell components. Dissolution in situ seems more likely, with cell remnants finding their way into the pigment epithelial cell's capable phagolysosomal system.

Histologic studies have shown that in the neural retina cone density decreases between the fourth and eighth decades.[25] The number of foveal cones was reported to be 96,900 to 281,000 per square millimeter in whole mounts of human retinas from donors aged 27 to 72 years in a small series.[25,26] These data cannot be compared with our morphometric data from tissue sections because both cones and rods were included in our 600-μm wide counting area. Nonetheless, the great variation in number of photoreceptors in normal subjects indicates a need for caution in interpreting low cell counts in eyes of old donors as indicative of age-related loss of cells. Weale[9] estimated human cone density to decline by 3% to 4% per decade. Based on this, and using our data from patients 49 to 68 years of age (mean, 307 foveal photoreceptor nuclei), we would expect to find 9% to 16% fewer photoreceptors, or 258 to 279 in patients over 90 years of age. Instead, our sample mean of 195 photoreceptors (Table 4) indicates a loss of about 37% from that of the younger sample. Individual variation obviously plays a significant part in such calculations.

References

1. Keunen, J. E. E., van Norren, D., and van Meel, G. J.: Density of foveal cone pigments at older age. Invest. Ophthalmol. Vis. Sci. 28:985, 1987.
2. Feeney, L.: Lipofuscin and melanin of human retinal pigment epithelium. Fluorescence, enzyme cytochemical and ultrastructural studies. Invest. Ophthalmol. Vis. Sci. 17:583, 1978.
3. Sarks, S. H.: Ageing and degeneration in the macular region. A clinicopathological study. Br. J. Ophthalmol. 60:324, 1976.
4. Green, W. R.: Pathology of the Macula. In Spencer, W. H. (ed.): Ophthalmic Pathology. An Atlas and Textbook. Philadelphia, W. B. Saunders, 1985, pp. 924–1034.
5. Gass, J. D. M.: Stereoscopic Atlas of Macular Diseases. St. Louis, C. V. Mosby, 1987, pp. 24–97.
6. Burns, R. P., and Feeney-Burns, L.: Clinicomorphologic correlations of drusen of Bruch's membrane. Trans. Am. Ophthalmol. Soc. 78:206, 1980.
7. Sarks, S. H., VanDriel, D., Maxwell, L., and Killingsworth, M. C.: Softening of drusen and subretinal neovascularization. Trans. Ophthalmol. Soc. U.K. 100:414, 1980.
8. Penfold, P. I., Killingsworth, M. C., and Sarks, S. H.: Senile macular degeneration. The involvement of immunocompetent cells. Graefes Arch. Clin. Exp. Ophthalmol. 223:69, 1985.
9. Weale, R. A.: Retinal senescence. In Osborne, N. and Chader, G. (eds.): Progress in Retinal Research. Oxford, Pergamon Press, 1986, pp. 53–73.
10. Gartner, S., and Henkind, P.: Aging and degeneration of the human macula. 1. Outer nuclear layer and photoreceptors. Br. J. Ophthalmol. 65:23, 1981.
11. Lai, Y.-L., Masuda, K., Mangum, M. D., Lug, R., Macrae, D. W., Fletcher, G., and Liu, Y.-P.: Subretinal displacement of photoreceptor nuclei in human retina. Exp. Eye Res. 34:219, 1982.
12. Marshall, J., Grindle, J., Ansell, P. L., and Borwein, B.: Convolution in human rods. An ageing process. Br. J. Ophthalmol. 63:181, 1979.
13. Tucker, G. S.: Refractile bodies in the inner segments of cones in the aging human retina. Invest. Ophthalmol. Vis. Sci. 27:708, 1986.
14. Iwasaki, M., and Inomata, H.: Lipofuscin granules in human photoreceptor cells. Invest. Ophthalmol. Vis. Sci. 29:671, 1988.
15. Young, R. W.: Pathophysiology of age-related macular degeneration. Surv. Ophthalmol. 31:291, 1987.
16. ———: Solar radiation and age-related macular degeneration. Surv. Ophthalmol. 32:252, 1988.
17. Tso, M. O. M., and Friedman, E.: The retinal pigment epithelium. III. Growth and development. Arch. Ophthalmol. 80:214, 1968.
18. Streeten, B. W.: Development of the human

retinal pigment epithelium and the posterior segment. Arch. Ophthalmol. 81:383, 1969.

19. Dorey, K. C., Wu, G., Ebenstein, D., Garsd, A., and Weiter, J. J.: Cell loss in the aging retina. Relationship to lipofuscin accumulation and macular degeneration. Invest. Ophthalmol. Vis. Sci. 30:1691, 1989.

20. Katz, M. L., and Robison, W. G., Jr.: Age-related changes in the retinal pigment epithelium of pigmented rats. Exp. Eye Res. 38:137, 1984.

21. Weiter, J. J., Delori, F. C., Wing, G. L., and Fitch, K. A.: Retinal pigment epithelial lipofuscin and melanin and choroidal melanin in human eyes. Invest. Ophthalmol. Vis. Sci. 27:145, 1986.

22. Feeney-Burns, L., Neuringer, M., and Gao, C.-L.: Macular pathology in monkeys fed semipurified diets. In LaVail, M. M. (ed.): Inherited and Environmentally Induced Retinal Degenerations. New York, Alan R. Liss, 1989, pp. 601–622.

23. Shoch, N. W.: Longitudinal studies of aging in humans. In Finch, C. E., and Schneider, E. L.: Handbook of the Biology of Aging. New York, Van Nostrand Reinhold, 1985, pp. 721–743.

24. Weale, R. A.: A Biography of the Eye. London, H. K. Lewis, 1982, pp. 242–253.

25. Yuodelis, C., and Hendrickson, A.: A qualitative and quantitative analysis of the human fovea during development. Vision Res. 26:847, 1986.

26. Curcio, C. A., Sloan, K. R., Jr., Packer, O., Hendrickson, A. E., and Kalina, R. E.: Distribution of cones in human and monkey retina. Science 236:579, 1987.

OPHTHALMIC MINIATURE

Mrs. Dubedat: Doctor: you must save my husband. You must . . . .

Ridgeon (huffily): I am not a curemonger: if you want cures, you must go to the people who sell them. (Recovering himself, ashamed of the tone of his own voice) But I have at the hospital ten tuberculous patients whose lives I believe I can save.

Mrs. Dubedat: Thank God!

Ridgeon: Wait a moment. Try to think of those ten patients as ten shipwrecked men on a raft—a raft that is barely large enough to save them—that will not support one more. Another head bobs up through the waves at the side. Another man begs to be taken aboard. He implores the captain of the raft to save him. But the captain can only do that by pushing one of his ten off the raft and drowning him to make room for the new comer. That is what you are asking me to do.

George Bernard Shaw, *The Doctor's Dilemma,*
Complete Plays and Prefaces
New York, Dodd, Mead & Company, 1963, p. 113

The Pattern Electroretinogram in Diabetes

Thomas C. Prager, Ph.D., Charles A. Garcia, M.D., Caroline A. Mincher, B.S., Jasleen Mishra, Ph.D., and Hshuan-Ho Chu, M.D.

In 27 normal subjects and 64 insulin-dependent diabetic patients, we evaluated the pattern electroretinogram, which may reflect the neural activity of the spatially sensitive retinal ganglion cells. The amplitude of the pattern electroretinogram was reduced in diabetic patients who had no observable retinal changes. The amplitude was further reduced with increasing retinopathy. The pattern electroretinogram amplitude change was a more sensitive indicator of retinal change among the diabetic subpopulations than the statistically significant changes in latency. A significant correlation between pattern electroretinogram amplitude and the duration of diabetes were found in diabetic patients with either no observable retinopathy or minimal background retinopathy. The pattern electroretinogram may be useful as a quantitative, dependent variable to establish and monitor short-term metabolic and physiologic changes in diabetic patients.

SEVERAL RESEARCHERS have investigated the pattern electroretinogram in diabetic populations with equivocal results. Arden, Hamilton, and Wilson-Holt[1] suggested that in diabetic patients, the pattern electroretinogram amplitude deteriorates with decreasing retinal capillary circulation. These investigations found the pattern electroretinogram amplitude to be normal in diabetic patients with microaneurysms. Although another study[2] found the pattern electroretinogram amplitude to be normal in patients with minimal retinal changes, the latency of the pattern electroretinogram has been found to be abnormal in 5.9% of diabetic patients without retinopathy.[3]

By slightly modifying the basic technique used to record the pattern electroretinogram, we have developed a relatively simple procedure that allows the distinction of diabetic patients who have no observable retinopathy from normal subjects. We demonstrate that a reduction in pattern electroretinogram amplitude significantly correlates with the duration of diabetes. Patients with mild and moderate background retinopathy had significantly more attenuated pattern electroretinogram amplitudes than diabetic patients without fundus changes.

Subjects and Methods

A total of 27 normal subjects were compared to 64 insulin-dependent diabetic patients. The control population, which consisted of 13 men and 14 women with an average age of 31.04 years (S.D., 9.95), was compared to 64 diabetic patients who ranged in age from 18 to 65 years (mean, 41.03 years: S.D., 12.06). There was not a significant difference in pattern electroretinogram amplitude over years in the control population (r = .15, F = 0.58, P = .45). Of the diabetic population, 28 patients were female (mean age, 39.79 years: S.D., 12.63) and 36 were male (mean age, 42.00 years: S.D., 13.31).

The 107 diabetic eyes were independently graded according to severity of retinopathy. Color stereoscopic fundus photographs taken in the seven standard fields provided the basis for placement into one of three groups. A total of 38 diabetic eyes had no observable retinopathy. A classification of mild background retinopathy (N = 34) required that there be less than 30 microaneurysms throughout the fundus (essentially equivalent to Early Treatment

Accepted for publication Dec. 6, 1989.

From the Department of Ophthalmology, University of Texas Medical School, Houston, Texas. This study was supported in part by the Lions Club International Research program of the American Diabetes Association, the Vale-Asche Foundation, and the Hermann Eye Fund. This study was presented in part at the Association of Research in Vision and Ophthalmology annual meeting, May 5, 1989.

Reprint requests to Thomas C. Prager, Ph.D., Hermann Eye Center, 6411 Fannin St., Houston, TX 77030.

Diabetic Retinopathy Study classification P0), whereas the moderate background retinopathy group (N = 35) included those eyes with greater than 30 microaneurysms, or small dot and blot hemorrhages or rare cotton wool spots or both (similar to Early Treatment Diabetic Retinopathy Study classification P1). None of the diabetic patients had macular edema. All subjects in this investigation had visual acuity of 20/30 or better.

For statistical analysis, the mean value for both control eyes was used as datum, because evoked-potential data from both eyes of normal subjects would be expected to correlate highly with each other. Because retinopathy is sometimes asymmetric, data from diabetic eyes were treated as independent events. Categorization of fundus photographs from the 58 diabetic patients in this study who had data from both eyes showed that 17 of 58 (29.31%) of these subjects had different degrees of retinopathy between eyes. Three or more replications of the evoked potential were obtained for each eye. All evoked potentials were required to be within 10% of the largest amplitude to be acceptable data. Every subject signed an informed consent form that had been approved by the Committee for the Protection of Human Subjects, the University of Texas Medical School at Houston.

The patient inclusion criteria included the following: age under 65 years: no history of cardiovascular, neurologic, or ocular disease (except diabetic retinopathy): no test eye previously treated by laser or cryopexy for retinal disease: no test eye with previous surgery, such as vitrectomy or cataract extraction: and best-corrected visual acuity of at least 20/80.

After the instillation of a topical anesthetic (proparacaine hydrochloride), pattern electroretinograms were recorded using the X-Static/DTL corneal thread electrode[4,5] placed in the lower cul-de-sac and secured to the nasal canthus with Vaseline. The electrode holder, a modified alligator clip shielded by plastic, allowed the use of a fresh strand of electrode thread for each test. Conductive paste was used to place the reference electrode on the ipsilateral temple,[6] and a spring-loaded ground lead was attached to the ear lobe. The eye not being tested was patched[7,8] with opaque fabric, and the subject was instructed to keep the loosely patched occluded eye open. Volumetric electrical conduction from squinting eyelid muscles has been noted to generate artifact,[9] significantly reducing the signal-to-noise ratio. Electrical impedance was less than 5,000 Ω and was checked by instructing the patient to look up to ensure that the active electrode was on the sclera, not the cornea. Patients' pupils were not dilated,[10] and all subjects wore their full spectacle correction, if necessary, to ensure sharp image focus on the retina and to maximize the evoked potential.[11] In pilot studies, the movement of contact lenses against the thread electrode caused excessive artifact. Patients with contact lenses removed them and wore the appropriate spectacle correction.

Patient fixation and alertness were ensured by having the subject intermittently direct the beam from a laser pointer onto a small fixation target located in the center of the viewing monitor. The benefits of the laser pointer are important: loss of attention because of defocusing after repetitious patterned stimuli attenuates pattern electroretinogram amplitude. Giving the patient a task maintains alertness and maximizes the evoked potential. The laser pointer also permits the investigator to readily check the subject's fixation.

A counterphasing, high-contrast, black-and-white checkerboard (98%) array was generated by a visual stimulator. Individual checks subtended a visual angle of 0.5 degree at 140 cm. The overall checkerboard pattern stimulated the central 16 degree × 19 degree retina with a cycle reversal rate of 8.3 Hz (16.6 reversals/sec).

Two hundred stimulations were averaged with an analysis time of 125 msec and bandpass filtered 1 to 100 Hz. The test was repeated two or three times, with each of the waveforms having amplitudes within 10% of one another. The waveforms then were combined into a single evoked potential, which was reported as datum. Recording time was approximately ten to 15 minutes per eye.

Results

The likelihood of retinal metabolic or structural changes increases with disease duration, a fact which is reflected in a decrease in the amplitude of pattern electroretinogram as the disease progresses. To establish the significance of this relationship, normal subjects were contrasted to each of the three diabetic groups by separate one-way analyses of variance for both amplitude and latency values. Table 1 summarizes N, mean, S.D., F values, and probability for the various groups. Change in the pattern

TABLE 1
STATISTICAL SUMMARY OF NORMAL SUBJECTS' AND DIABETIC PATIENTS' PATTERN ELECTRORETINOGRAM AMPLITUDE AND LATENCY VALUES

				ANALYSES OF VARIANCE	
GROUP	N	$\bar{X}$	S.D.	F	P*
Normal patients					
Amplitude	27	3.26 μV	(0.70)	—	—
Latency	27	62.25 msec	(4.39)	—	—
Diabetic patients					
No retinopathy					
Amplitude	38	2.60 μV	(0.92)	9.94	.0025
Latency	38	65.30 msec	(4.35)	7.64	.0075
Mild background diabetic retinopathy					
Amplitude	34	2.29 μV	(0.85)	23.00	<.0001
Latency	34	63.75 msec	(5.56)	1.30	.2582 (NS)
Moderate background diabetic retinopathy					
Amplitude	35	2.00 μV	(0.80)	41.79	<.0001
Latency	29	64.79 msec	(4.23)	5.27	.0252

*NS indicates not significant.

electroretinogram amplitude was a more sensitive index of retinal changes than latency data, although both measurements were significantly different from the measurements of normal subjects. The mean (± S.D.) pattern electroretinogram amplitude values from the four groups (Fig. 1) were: normal subjects, 3.26 μV (± 0.70): subjects with no retinopathy, 2.60 μV (± 0.92): subjects with minimal retinopathy, 2.29 μV (± 0.85): and subjects with moderate retinopathy, 2.00 μV (± 0.80). As the degree of retinopathy increases, the significance level for amplitude reductions also increases. Diabetic patients with no observable retinopathy differed significantly from normal subjects ($P = .0025$). The F value changed from 9.94 to 23.00 ($P < .0001$) when normal subjects were contrasted to diabetic patients with minimal background retinopathy (< 30 microaneurysms) and increased markedly when comparing normal subjects to diabetic patients who had more than 30 microaneurysms ($F = 41.79$, $P < .0001$). The pattern electroretinogram amplitudes for diabetic patients without retinopathy were also significantly different from diabetic patients who had more than 30 microaneurysms ($F = 8.53$, $P = .0047$). The probability of abnormality for any single individual may be readily calculated by determining a Z score (amplitude score − mean normal subjects/S.D. normal subjects) then referring to a probability table of normal curve areas.

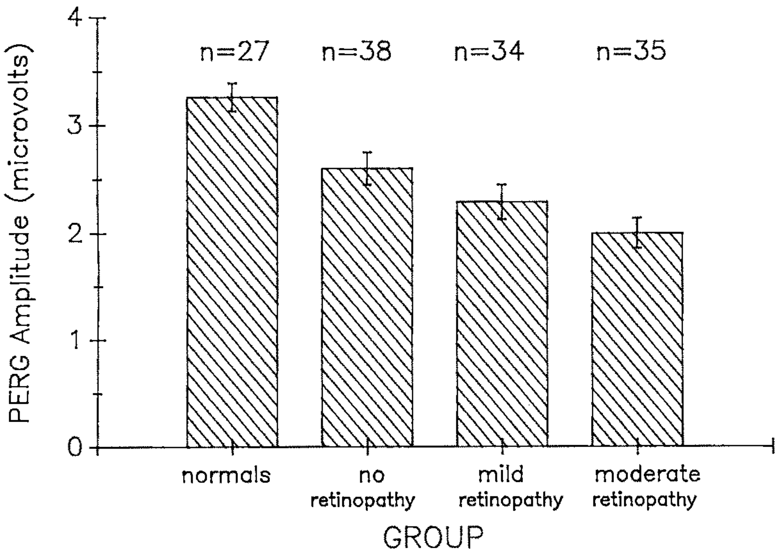


Fig. 1 (Prager and associates). Average pattern electroretinogram amplitude (microvolts) ± 1 standard error for normal subjects, and diabetic patients with no, mild, or moderate retinopathy.

TABLE 2
STATISTICAL SUMMARY OF RELATIONSHIP BETWEEN PATTERN ELECTRORETINOGRAM AMPLITUDE AND DURATION OF DIABETES FOR THREE DIABETIC GROUPS

GROUP	$\bar{X}$	S.D.	r	ANALYSES OF VARIANCE F	P*
No retinopathy					
Duration	7.63 yrs	(5.30)	—	—	—
Amplitude	2.60 μV	(0.92)	—	—	—
Correlation	—	—	−0.46	9.42	.0041
Mild background diabetic retinopathy					
Duration	14.65 yrs	(8.20)	—	—	—
Amplitude	2.29 μV	(0.85)	—	—	—
Correlation	—	—	−0.56	14.45	.0006
Moderate background diabetic retinopathy					
Duration	19.06 yrs	(5.17)	—	—	—
Amplitude	2.00 μV	(0.80)	—	—	—
Correlation	—	—	0.26	2.57	.1186 (NS)

*NS indicates not significant.

A linear regression analysis was performed for each diabetic group to determine the correlation between pattern electroretinogram amplitude and duration of the disease (Table 2). The greatest correlation occurred in the diabetic groups with no retinopathy ($r = -.46$, P = .0041) or minimum background retinopathy ($r = -.56$, P = .0006). Individual pattern electroretinogram amplitude values plotted against duration for the diabetic patients with no retinopathy are depicted in Figure 2. A line of best fit is drawn through the data. The diabetic patients with moderate retinopathy showed the lowest correlation, .26, which was not significant (P = .12). Although the variance for the three diabetic groups is similar (S.D./group mean), the slope for the moderate background retinopathy group is not as steep as those found in the other two diabetic groups. This difference accounts for the poor correlation between duration of diabetes and amplitude of the pattern electroretinogram in the moderate background retinopathy group.

To assess test-retest reliability, five subjects were tested on three separate days. The average, average difference over days, and percent average difference for amplitude and latency are summarized in Table 3. Individual and summed data are shown. The average difference in microvolts over days was 0.14 μV, which is an average change of 4%. The average differ-

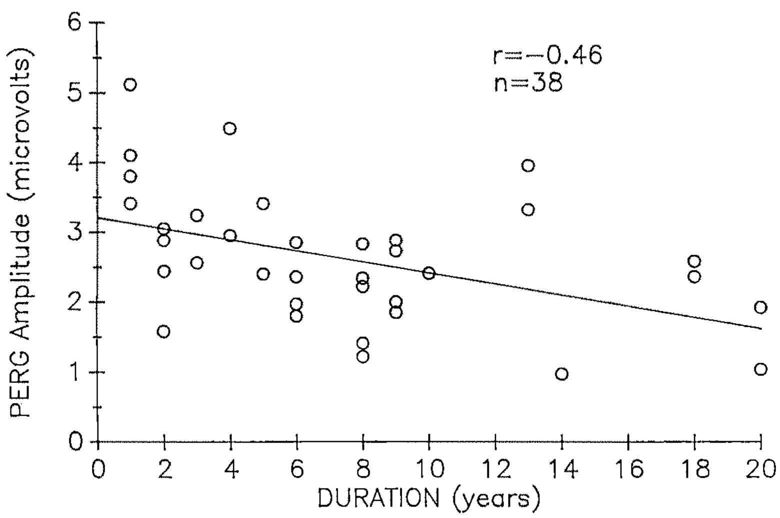


Fig. 2 (Prager and associates). Duration (years) of diabetes vs pattern electroretinogram amplitude (microvolts) in diabetic patients with no observable retinopathy. A line of best fit has been drawn through the scattergram.

TABLE 3
TEST-RETEST RELIABILITY OF THE PATTERN ELECTRORETINOGRAM

AMPLITUDE MEASUREMENTS							LATENCY MEASUREMENTS						
	DAY				AVERAGE DIFFERENCE			DAY				AVERAGE DIFFERENCE	
SUBJECT NO.	1	2	3	AVERAGE (μV)	μV	%	SUBJECT NO.	1	2	3	AVERAGE (MSEC)	MSEC	%
1	3.95	3.90	3.95	3.93	0.02	0.56	1	57.00	59.75	60.25	59.00	1.33	2.26
2	3.12	2.92	3.02	3.02	0.07	2.21	2	61.50	61.50	63.25	62.08	0.78	1.25
3	3.12	3.12	3.41	3.22	0.13	4.01	3	66.00	64.50	61.25	63.92	1.78	2.78
4	4.00	3.80	3.51	3.77	0.17	4.60	4	56.25	65.00	62.25	61.17	3.28	5.36
5	4.00	3.17	3.66	3.61	0.29	8.13	5	56.75	56.75	58.00	57.17	0.56	0.97
Group average	—	—	—	3.51	0.14	3.90	Group average	—	—	—	60.67	1.54	2.52
Range							Range						
Minimum	—	—	—	3.02	0.02	0.56	Minimum	—	—	—	57.17	0.56	0.97
Maximum	—	—	—	3.93	0.29	8.13	Maximum	—	—	—	63.92	3.28	5.36

ence for each subject ranged from 0.02 μV to 0.29 μV.

Discussion

We found the pattern electroretinogram to be abnormal in diabetic patients who had no observable retinal changes. The amplitude of the pattern electroretinogram decreases with increasing retinopathy. Although statistically significant changes in latency were observed, the pattern electroretinogram amplitude change was a more sensitive indicator of retinal change among the diabetic subpopulations. Significant correlations between pattern electroretinogram amplitude and duration of diabetes were found in diabetic patients who had no observable retinopathy or minimal background retinopathy. The correlation between duration and pattern electroretinogram amplitude was not significant in diabetic patients who had moderate retinopathy, because by the time retinopathy has advanced to later stages, most patients already have a reduction in amplitude. These findings suggest that the pattern electroretinogram, a 20-minute, noninvasive test, may be useful as a quantitative, dependent variable to monitor short-term metabolic and physiologic changes in drug treatment studies conducted in diabetic populations. Previous studies have categorized observable retinal changes, but often have neglected diabetic populations without demonstrable retinopathy. Pattern electroretinography may be useful in detecting subtle changes in this population before gross anatomic changes occur. Additionally, the pattern electroretinogram may have important clinical application as a screening test to identify patients who are at risk for developing further retinopathy. By determining a Z score, the probability for abnormality may be readily computed for an individual patient.

The pattern electroretinogram is relatively simple to record. The ability to accurately monitor abnormal pattern electroretinogram amplitudes in populations with no or minimal retinal changes depends on procedure. To reduce variability and artifact, we used a thread electrode secured to the inner canthus with Vaseline: full spectacle correction[11]: reference electrode placement on the ipsilateral temple[6]: and a laser pointer to ensure patient attention and fixation. These procedural details and the requirement that all acceptable replication data be within 10% of an individual's largest pattern electroretinogram amplitude may explain why we, in contrast to other investigators,[9] were able to make subtle distinctions in diabetic populations that had no observable retinopathy or minimum retinopathy.

The pattern electroretinogram may be a quick, reliable, and predictive test to indicate which patients are at risk for developing further retinopathy. The test appears to be most sensitive in diabetic patients who have no or minimal diabetic changes. Our findings suggest that electrophysiologic amplitude reductions, reflecting subtle impairment in retinal function,

may occur before ophthalmoscopically visible changes are noted. Although the potential application of the pattern electroretinogram as a screening test and measure of efficacy of various drug and treatment regimens has great potential, prospective longitudinal studies need to be performed and replicated before the pattern electroretinogram becomes a routine clinical test for evaluating diabetic patients.

References

1. Arden, G., Hamilton, M., and Wilson-Holt, J.: Pattern electroretinograms become abnormal when background diabetic retinopathy deteriorates to a preproliferative stage. Possible use as a screening test. Br. J. Ophthalmol. 70:330, 1986.
2. Coupland, S.: A comparison of oscillatory potential and pattern electroretinogram measures in diabetic retinopathy. Doc. Ophthalmol. 66:207, 1987.
3. Trick, G., Burde, R., Gordon, M., Kilo, C., and Santiago, J.: Retinocortical conduction time in diabetics with abnormal pattern reversal electroretinograms and visual evoked potentials. Doc. Ophthalmol. 70:19, 1988.
4. Dawson, W., Trick, G., and Litzkow, C.: Improved electrode for electroretinography. Invest. Ophthalmol. Vis. Sci. 18:988, 1979.
5. Dawson, W., Trick, G., and Maida, T.: Evaluation of DTL corneal electrode. Doc. Ophthalmol. Proc. Ser. 31:81, 1982.
6. Hess, R., and Baker, C.: Assessment of retinal function in severely amblyopic individuals. Vision Res. 24:1367, 1984.
7. Seiple, W., and Siegel, I.: Recording the pattern electroretinogram. A cautionary note. Invest. Ophthalmol. Vis. Sci. 24:796, 1983.
8. Peachey, N., Sokol, S., and Moskowitz, A.: Recording the contralateral PERG. Effect of different electrodes. Invest. Ophthalmol. Vis. Sci. 24:1514, 1983.
9. Mishra, J., Reszel, E., and Prager, T.: Effect of squinting on the pattern-electroretinogram. Am. J. Ophthalmol. 108:744, 1989.
10. Hawkes, C., and Stow, B.: Pupil size and the pattern evoked visual response. J. Neurol. Neurosurg. Psychiatry 44:90, 1981.
11. Millodot, M., and Riggs, R. L.: Refraction determined electrophysiologically. Responses to alteration of visual contours. Arch. Ophthalmol. 84:272, 1970.

OPHTHALMIC MINIATURE

The features are delicately modelled, if claiming no regularity of beauty, and although the face is lacking in mobility, as we think of the term, there appeared to me a sense of the mind's attentiveness and color, (if I may so put it) traceable under the mask-like expression, mask-like except for the eyes, which register the reaction of each moment . . . .Mr. Woolf was at my right, as thin as she, but much less tall: the face is almost emaciated, the features very aquiline but not necessarily Hebraic, the expression warmer than hers [Virginia Woolf], especially the eyes which to me revealed a number of qualities, as patience, weariness and isolation.

Lyndall Gordon, *Eliot's New Life*
New York, Farrar Straus Giroux, 1988, p. 163

Twin Vessels in Familial Retinal Cavernous Hemangioma

Ferdinando Bottoni, M.D., Maria P. Canevini, M.D., Raffaele Canger, M.D., and Nicola Orzalesi, M.D.

We investigated the presence of twin vessels in two patients and in four of their relatives at risk from one family with autosomal-dominant hereditary cavernous hemangioma of the retina associated with central nervous system involvement. Twin vessels were detected in four of the six patients examined. The proband had bilateral retinal vascular hamartomas with central nervous system involvement but no twin vessels. The proband's mother had vascular hamartomas of the retina and brain with twin vessels. In the other three family members, twin vessels were associated either with retinal cavernous hemangiomas (one patient) or with normal fundi (two patients). Because twin vessels may be an ocular manifestation of von Hippel-Lindau disease, their presence in one of our two patients and in the otherwise healthy three family members suggests that twin vessels may be associated with different retinal vascular hamartomas, including capillary and cavernous hemangiomas.

Cavernous hemangioma of the retina is an unusual vascular hamartoma of the inner retinal layers that clinically shows clumps of thin-walled saccular aneurysms filled with dark blood. The tumor may vary from a rather uncomplicated collection of aneurysms to an elaborate, sessile, racemose complex projecting into the vitreous cavity.[1] The hamartomatous lesion, usually unilateral, steady in size, and not associated with evident exudation, is often covered by a gray-white fibroglial membrane.[2]

After Weskamp and Cotlier's[3] report of cavernous angiomas of the retina associated with similar lesions of the skin and brain, a neuro-oculocutaneous syndrome was established by Gass and a number of other investigators.[4-11] Thus far, more than 54 persons from 17 families with cavernous malformations of the central nervous system and retina have been studied, and the cutaneous vascular lesions have been an inconsistent manifestation.[12] Autosomal-dominant inheritance with high penetrance and variable expression has been confirmed.[13]

Twin vessels are paired retinal arterioles and venules separated by less than one venule width, located at least two disk diameters from the disk and extending for a distance of more than one disk diameter.[14] They have been recently described in patients with von Hippel-Lindau disease and their at-risk family members, in whom they may represent an early diagnostic sign of the disease.[14]

We studied a family with familial cavernous malformations of the central nervous system and retina that included three affected persons from three generations. Twin vessels were observed in four of the six examined family members.

Case Reports

Case 1 (III-1)

The proband was an 11-year-old boy (Fig. 1) whose grandfather died of unknown causes. At the age of 54 years, the grandfather had been operated on for an endocranial hypertension syndrome caused by a left cerebellar cavernous angioma that was removed and diagnosed histologically. The proband had experienced his first seizure (head and eyes turned to the right, loss of consciousness) at 8 years of age. An electroencephalogram showed no abnormalities. Computed tomographic scans disclosed multiple, small, partially calcified lesions in the deep white matter and in the cerebellum, and a larger, hyperdense, minimally enhancing lesion in the left posterior frontal region. At that time, the patient was referred to a local ophthalmologist who diagnosed a toxoplasmic reti-

Accepted for publication Dec. 1, 1989.

From the Eye Clinic (Drs. Bottoni and Orzalesi) and the Epilepsy Center (Drs. Canevini and Canger), Institute of Biomedical Sciences, S. Paolo Hospital, University of Milan, Milan, Italy.

Reprint requests to Ferdinando Bottoni, M.D., Via Andrea Verga 4, 20144 Milano, Italy.

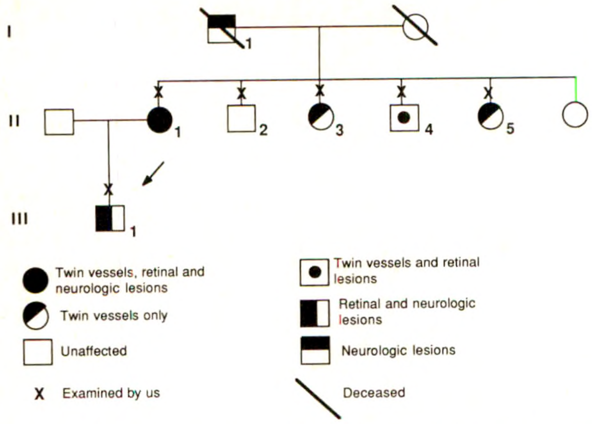


Fig. 1 (Bottoni and associates). Pedigree of family with familial cavernous malformations. The proband is indicated by an arrow.

nochoroiditis with macular involvement that caused visual loss in his right eye.

At age 9 years, the proband began to have simple partial seizures involving the right arm or the right side of the face, or both, with a frequency of about ten seizures per month. Subsequently, seizures with tonic symptoms in the right upper and lower limbs, with loss of consciousness and a slow fall backwards, occurred. After the seizures, the patient was frequently aphasic.

The patient was first seen at the Epilepsy Center of our institution at 10 years of age. Carbamazepine monotherapy was started, which resulted in a reduction in seizure frequency. Examination disclosed no focal neurologic deficits, and an electroencephalogram showed no abnormalities. We examined the patient one year later, at which time his visual acuity was R.E.: 20/50 and L.E.: 20/20. Results of external and slit-lamp examinations were normal. Ophthalmoscopy of the right eye disclosed some large, dark, saccular aneurysms in the macula, whose anterior surface was partly covered by a pigmented fibrous membrane. There was no exudation in the macular area, and the adjacent retinal blood vessels appeared unaffected (Fig. 2). The left eye showed microaneurysms nasal to the optic disk with plasma-erythrocytic separation (Fig. 2).

Fluorescein angiography demonstrated delayed and incomplete perfusion of the lesions with plasma/erythrocyte layering within the intraretinal aneurysms. There were no twin vessels in either eye.

Physical examination showed no cutaneous vascular hamartomas. The results of serologic tests for toxoplasmosis were negative. A 0.5-T (tesla) magnetic resonance imaging of the brain showed the same lesions demonstrated by computed tomography: the largest lesion was characterized by an irregular signal in intermediate and T_2-weighted images, surrounded by a hypointense halo (Fig. 3). Magnetic resonance imaging also showed multiple (more than 40), scattered infratentorial and supratentorial small lesions, with a hypointense signal in intermediate and T_2-weighted images (Fig. 3). A computed tomography of the abdomen showed no abnormalities. Cerebral angiography showed no abnormalities with the exception of an avascu-

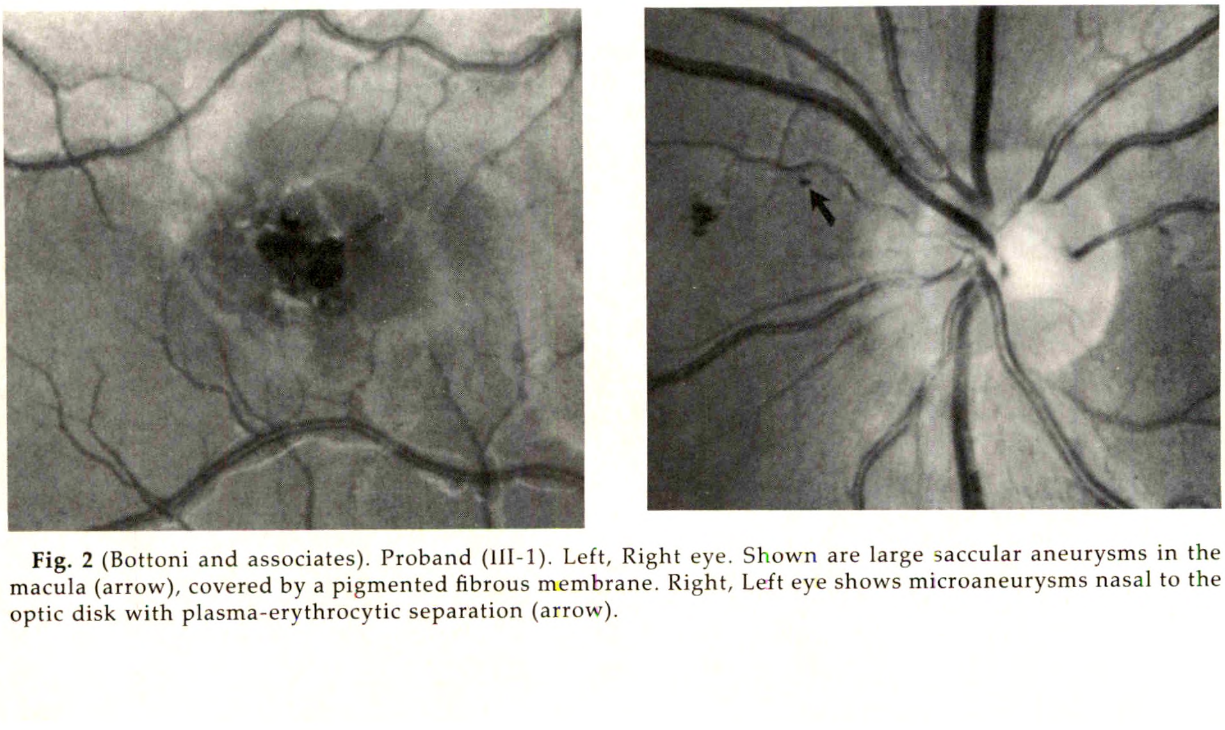


Fig. 2 (Bottoni and associates). Proband (III-1). Left, Right eye. Shown are large saccular aneurysms in the macula (arrow), covered by a pigmented fibrous membrane. Right, Left eye shows microaneurysms nasal to the optic disk with plasma-erythrocytic separation (arrow).

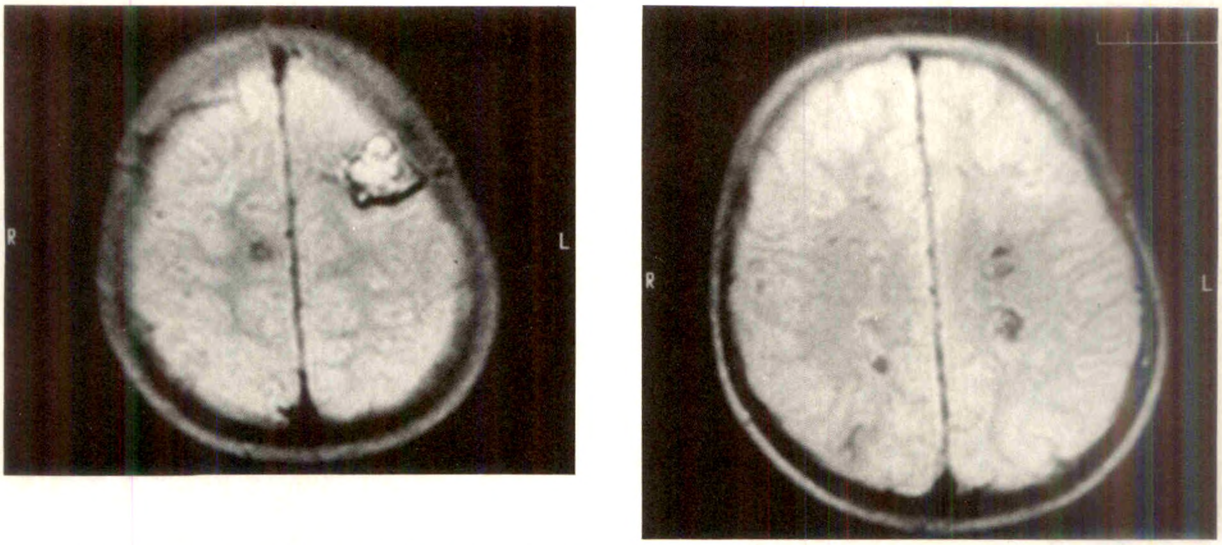


Fig. 3 (Bottoni and associates). Proband (III-1). Left, Magnetic resonance imaging (spin echo, repetition time [TR], 1,820 msec, echo time [TE], 50 msec) discloses a large, high-signal intensity lesion in the left frontal lobe, surrounded by a hypointense halo. Right, Multiple scattered hypointense lesions in the white matter are also demonstrated.

lar area in the same region of the large frontal lesion demonstrated by both computed tomography and magnetic resonance imaging. A diagnosis of multiple cavernous hemangiomas of the retina and central nervous system was eventually established.

Case 2 (II-1)

The proband's 38-year-old mother had a six-year history of seizures (uncontrolled by different high-dose monotherapies and polytherapies) and ultimately began to have frequent, prolonged complex partial seizures (one to two hours' duration).

The patient's visual acuity was 20/20 in both eyes. Fluorescein angiography of the left fundus disclosed a one-disk diameter hyperfluorescent lesion in the superotemporal quadrant, which was partly covered by a masking pigmented membrane (Fig. 4). Paired vessels, one retinal arteriole, and one venule running a parallel course for more than one disk diameter were seen along the superior vascular arcade in both eyes (Fig. 5). The paired vessels were always located more than two disk diameters from the disk and showed normal circulation times. There was no vascular staining in the late phase, and there were no hemorrhages or exudates in their vicinity.

Neurologic and physical examination disclosed neither focal neurologic deficits nor cutaneous vascular lesions. Interictal electroencephalogram showed no focal abnormalities. Results of serologic testing for toxoplasmosis were negative. Magnetic resonance imaging scans disclosed more than 30 small lesions that had signal characteristics similar to those observed in her son; they were located in the right and left cerebellar hemisphere and in the pons, and they were also scattered in supratentorial regions, mainly in the right mesial temporal lobe, with complete alteration of the hippocampal structures.

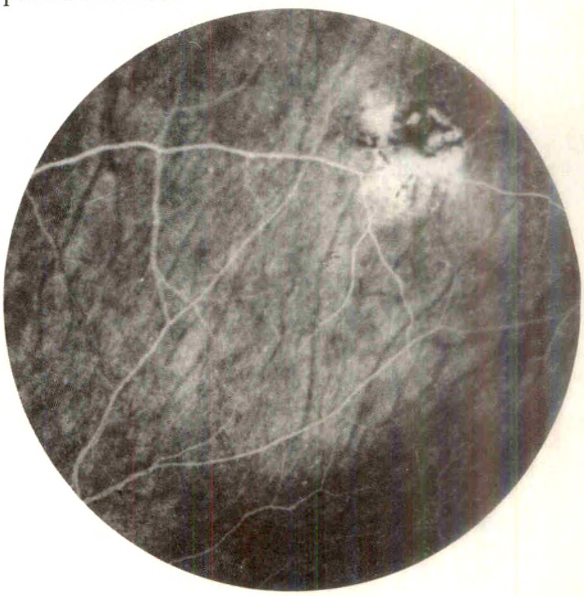


Fig. 4 (Bottoni and associates). Proband's mother (II-1), left eye. The fluorescein angiogram shows the one-disk diameter hyperfluorescent area in the superotemporal quadrant. A pigmented membrane overlies the anterior surface of the lesion.

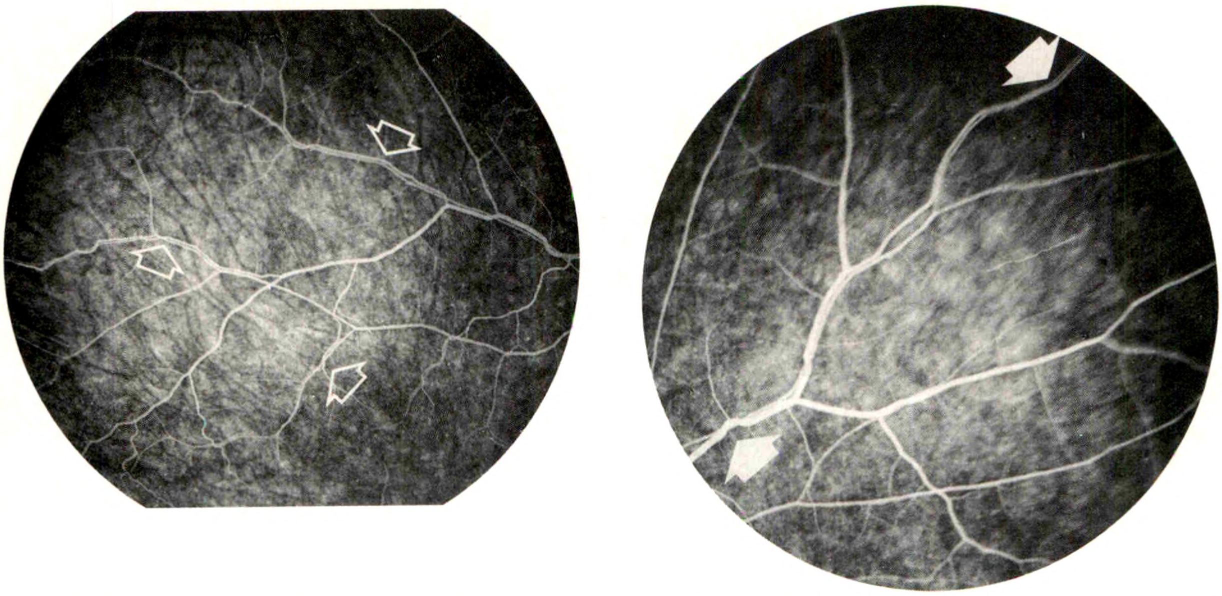


Fig. 5 (Bottoni and associates). Proband's mother (II-1). Left, Right eye. Fluorescein angiogram of twin vessels (arrows). Right, Angiogram of twin vessels along the superior vascular arcade in the left eye (between arrows).

Other family members—Three of the four family members we examined (Fig. 1) had twin vessels with normal visual acuity. The proband's maternal aunts (II-3 and II-5) had this feature in the superior nasal quadrant of the right eye, unassociated with retinal vascular hamartomas (one aunt [II-5] also complained of recurrent headaches). The proband's maternal uncle (II-4) had twin vessels along the major superior vascular arcade of the right eye, associated with a one-disk diameter retinal cavernous hemangioma in the inferior temporal quadrant of the same eye. All of these subjects, who had no major symptoms, refused neurologic and physical examinations.

Discussion

Retinal cavernous hemangiomas usually show peculiar clinical findings. The typical tumor is isolated from normal retinal circulation[1] and is composed of clumps of dark intraretinal aneurysms, which give a characteristic "cluster of grapes" appearance. Fluorescein angiography shows delayed and incomplete perfusion of the hamartoma with a typical plasma-erythrocyte separation within the vascular lesion. Dye will rarely extravasate from the tumor in the late phase of the angiogram because of the presence of normal endothelial cells and pericytes.[2] These findings can easily distinguish this vascular hamartoma from other retinal conditions, such as Coats' disease or Leber's miliary aneurysms, branch vein occlusion, diabetic retinopathy, von Hippel's disease, racemose hemangioma, and Rendu-Osler-Weber disease.

Nevertheless, when the tumor is located in the macula (10% of the cases[9]) and partly covered by a pigmented membrane, it can be misdiagnosed, as in our proband (III-1), who was referred to us with a diagnosis of toxoplasmic retinochoroiditis. Increase of the fibroglial component on the anterior surface of the tumor, possibly representing progressive thrombosis of some of the aneurysms,[9] may also be misleading. The atrophic appearance of the lesion in the proband's mother (II-1) illustrates this. Magnetic resonance imaging scans of the central nervous system and proper screening of the family members is mandatory in such patients to disclose the peculiar central nervous system involvement and autosomal-dominant inheritance of the disease.

The adult retinal vascular pattern is established several months after birth and matures during the next several years.[15] Larger arterioles and venules of the retina share a common territory but normally are not close to one another as are conjunctival or connective tissue vessels.[16] The staggered appearance of the normal retinal vessels was confirmed by De Yong and associates[14] who found a 5.5% prevalence of twin vessels in the normal population com-

pared with the 64% prevalence in patients with von Hippel-Lindau disease and their family members who are at risk.

The three-generation pedigree with retinal and central nervous system cavernous hemangiomas described herein is of interest because of the presence of twin vessels in four of the six family members examined (prevalence, 66%). As in pedigrees of families with von Hippel-Lindau disease,[14] twin vessels in our patients were associated with either retinal cavernous hemangiomas (II-1 and II-4) or with normal fundi (II-3 and II-5). Furthermore, the proband (III-1) had bilateral retinal vascular malformations but no twin vessels. Twin vessels have the properties of normal retinal vessels,[14] as shown by fluorescein angiography in our study (Fig. 5). To establish a definite association between twin vessels and cavernous hemangioma in our pedigree, it would have been necessary to find an obligate carrier with parent and offspring equally affected by cavernous hemangioma, exhibiting twin vessels as the only ophthalmoscopic sign. Nevertheless, the occurrence of twin vessels in the two different, dominantly inherited vascular hamartomas (retinal angiomatosis and cavernous hemangioma) would suggest a common pathogenic mechanism of both the retinal angiomas and the twin vessels, either of which originating from mesenchymal cells. Likewise, variability of retinal vascular hamartomas could explain either the presence or the absence of twin vessels in different family members. We believe that their occurrence is more likely to be an ocular manifestation accompanying vascular hamartomas than a trait of a separate gene, as suggested by De Yong and associates.[14]

Although heterozygotes with familial cavernous malformations of the central nervous system and retina may remain asymptomatic, they are at considerable risk for major neurologic complications (prevalence of intracranial hemorrhages, 48%).[12] Twin vessels may represent an additional useful ophthalmoscopic sign for family screening and early detection of family members who are at risk.

References

1. Gass, J. D. M.: Stereoscopic Atlas of Macular Diseases. Diagnosis and Treatment, ed. 3. St. Louis, C. V. Mosby, 1987, pp. 634–639.
2. Messmer, E., Font, R. L., Laqua, H., Hopping, W., and Naumann, G. O. H.: Cavernous hemangioma of the retina. Immunohistochemical and ultrastructural observations. Arch. Ophthalmol. 102:413, 1984.
3. Weskamp, C., and Cotlier, I.: Angioma del cerebro y de la retina con malformaciones capilares de la piel. Arch. Oftalmol. (Buenos Aires) 15:1, 1940.
4. Gass, J. D. M.: Cavernous hemangioma of the retina. A neuro-oculo-cutaneous syndrome. Am. J. Ophthalmol. 71:799, 1971.
5. Mildner, I.: Kavernose hamangiome der retina als symptom einer phakomatose. Ber. Dtsch. Ophthalmol. Ges. 71:610, 1971.
6. Gass, J. D. M.: Differential Diagnosis of Intraocular Tumors. A Stereoscopic Presentation. St. Louis, C. V. Mosby, 1974, p. 298.
7. Colvard, D. M., Robertson, D. M., and Trautmann, J. C.: Cavernous hemangioma of the retina. Arch. Ophthalmol. 96:2042, 1978.
8. Goldberg, R. E., Pheasant, T. R., and Shields, J. A.: Cavernous hemangioma of the retina. A four-generation pedigree with neurocutaneous manifestations and an example of bilateral retinal involvement. Arch. Ophthalmol. 97:2321, 1979.
9. Messmer, E., Laqua, H., Wessing, A., Spitznas, M., Weidle, E., Ruprecht, K., and Naumann, G. O. H.: Nine cases of cavernous hemangioma of the retina. Am. J. Ophthalmol. 95:383, 1983.
10. Schwartz, A. C., Weaver, R. G., Jr., Bloomfield, R., and Tyler, M. E.: Cavernous hemangioma of the retina, cutaneous angiomas, and intracranial vascular lesion by computed tomography and nuclear magnetic resonance imaging. Am. J. Ophthalmol. 98:483, 1984.
11. Pancurak, J., Goldberg, M. F., Frenkel, M., and Crowell, R. M.: Cavernous hemangioma of the retina. Genetic and central nervous system involvement. Retina 5:215, 1985.
12. Dobyns, W. B., Michels, V. V., Groover, R. V., Mokri, B., Trautmann, J. C., Forbes, G. S., and Laws, E. R., Jr.: Familial cavernous malformations of the central nervous system and retina. Ann. Neurol. 21:578, 1987.
13. Hayman, L. A., Evans, R. A., and Ferrell, R. E.: Familial cavernous angiomas. Natural history and genetic study over a 5-year period. Am. J. Med. Genet. 11:147, 1982.
14. De Yong, P. T. V. M., Verkaart, R. J. F., Van de Vooren, M. J., Majoor-Krakauer, D. F., and Wiegel, A. R.: Twin vessels in von Hippel-Lindau disease. Am. J. Ophthalmol. 105:165, 1988.
15. Wise, G. N., Dollery, C. T., and Henkind, P.: Development of retinal vessels. In The Retinal Circulation. New York, Harper and Row, 1971, pp. 1–18.
16. ———: Pattern and location of retinal vessels. In The Retinal Circulation. New York, Harper and Row, 1971, pp. 20–31.

Helicoid Peripapillary Chorioretinal Degeneration

Periklis D. Brazitikos, M.D., and Avinoam B. Safran, M.D.

Study of a father and son who had helicoid peripapillary chorioretinal degeneration suggests that a progressive tearing and retraction of the retinal pigment epithelium or of Bruch's membrane around the optic disk may be involved in the disorder's pathogenesis. We presume that this tearing results primarily from dysplastic abnormalities of the retinal pigment epithelium that surrounds the optic disk. The dystrophic lesions progress slowly and may affect the macula and even the peripheral retina.

HELICOID PERIPAPILLARY chorioretinal degeneration is a rare bilateral fundus disorder characterized by sharply demarcated, wing-like, radial, peripapillary atrophic areas of the retinal pigment epithelium and choriocapillaris, and the absence of inflammatory signs.[1-5] We examined a father and son who had this disorder. We suggest that the peripapillary retinal pigment epithelium undergoes progressive dehiscence and retraction in this condition.

Case Reports

Case 1

A 7-year-old boy was referred to us for ophthalmic examination. His general health was good, and results of the general examination were unremarkable. The best-corrected visual acuity with cycloplegic determined refraction was R.E.: 20/25 with -2.50×60 degrees and L.E.: 20/25 with -1.00×100 degrees. The ocular motility, results of anterior segment biomicroscopic morphologic examination, and intraocular pressure were normal. Ophthalmoscopy of each eye showed two wing-shaped areas of atrophy of the retinal pigment epithelium and choriocapillaris that extended from the optic disk toward the superonasal and inferonasal periphery (Fig. 1). The distal edge of the inferiorly directed atrophic area resembled a fishtail. In the left eye, a small triangular atrophic lesion with its base at the superotemporal border of the optic nerve head was present. The margins of the lesions were sharply demarcated. Pigmentation was slightly enhanced along the borders of the atrophic areas. Only the white background of the sclera and the large choroidal vessels could be seen within these lesions. Their floors were not ectatic. The overlying sensory retina did not show gliotic, dysplastic, or edematous changes. The optic disks were oval-shaped. The left optic disk showed an inferonasal tilting and a situs inversus of the emergence of the retinal vessels. The findings were nearly identical in both eyes (Fig. 1). The axial length, measured by biometry, was 23.2 mm for the right eye and 22.4 mm for the left eye.

Case 2

We examined the fundi of six members of the boy's family (Fig. 2) for evidence of a hereditary fundus abnormality. The only person who had helicoid peripapillary chorioretinal degeneration was the boy's father, aged 49 years, whose previous medical history was unremarkable. Visual acuity with cycloplegic determined refraction was R.E.: 20/25 with -2.00 -3.00×10 degrees and L.E.: 20/25 with -5.00 -2.00×0 degrees. Ocular motility, the anterior segment, and intraocular pressure were normal. Fundus examination of each eye showed two almost perpendicular wing-shaped atrophic lesions of the retinal pigment epithelium and choriocapillaris that extended from the nasal margin of the optic disk toward the nasal periphery. Adjacent to the temporal margin of the optic nerve head, a smaller irregular lesion was present. Within this smaller lesion, which

Accepted for publication Dec. 6, 1989.

From Clinique d'Ophtalmologie, Hôpital Cantonal Universitaire de Genève, Geneva, Switzerland. This study was presented as a poster at the annual meeting of the Swiss Society of Ophthalmology, St-Gall, Switzerland, Sept. 14–16, 1989.

Reprint requests to Periklis D. Brazitikos, M.D., Clinique d'Ophtalmologie, Hôpital Cantonal Universitaire de Genève, 22 rue Alcide-Jentzer, 1211 Geneva 4, Switzerland.

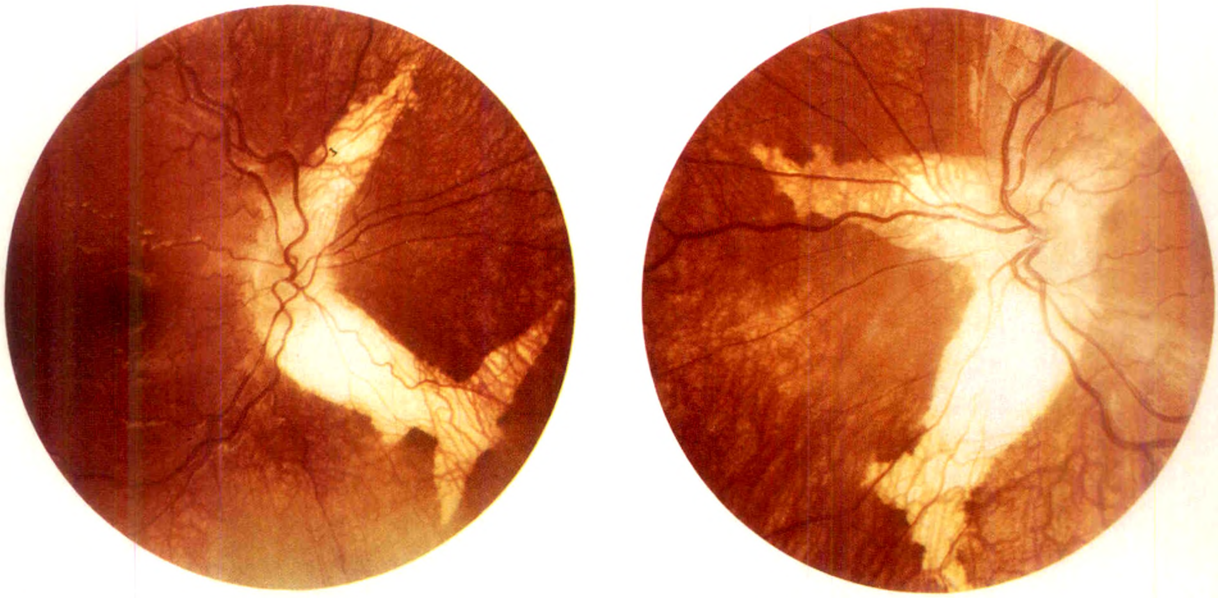


Fig. 1 (Brazitikos and Safran). Case 1. Fundi show the dystrophic lesions of retinal pigment epithelium and choriocapillaris extending from the optic disk toward the peripheral retina. Note the linear demarcation of these lesions, the absence of scarring and pigment clumping, the fishtail configuration of the inferior edges, and the slight enhancement of pigmentation along the margins.

reached the paramacular region, the choroid appeared normal. In the right eye, a small, round, atrophic chorioretinal lesion was present in the nasal side of the fundus, close to the upper defective wing-shaped area. Pigment accumulation and retinal edema were not observed, and the vitreous body was clear. The optic nerves appeared normal (Fig. 3). The patient refused fundus fluorescein angiography.

Discussion

Helicoid peripapillary chorioretinal degeneration is a rare bilateral ocular disorder characterized by wing-shaped, well-defined, atrophic areas of choriocapillaris and retinal pigment epithelium that radiate from the optic nerve head toward the macula and the fundus periphery. There are no inflammatory signs.[1-5]

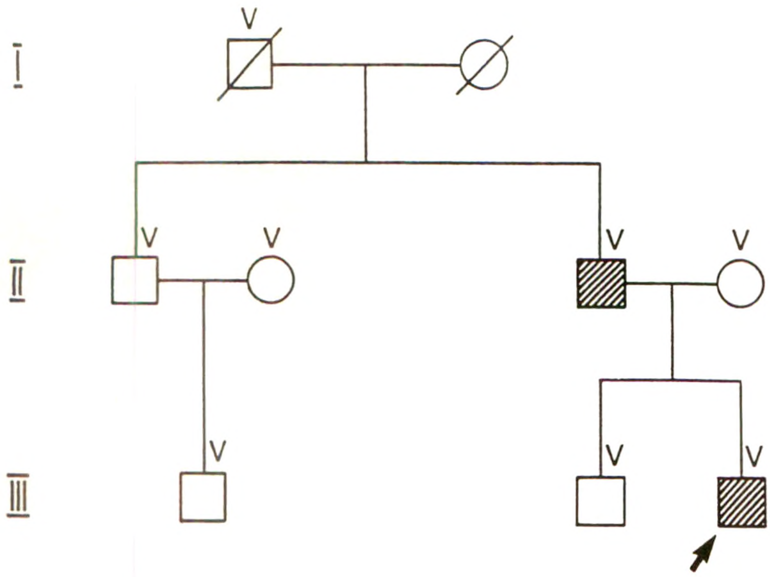


Fig. 2 (Brazitikos and Safran). Pedigree of the examined family. (The deceased man had been previously examined in our clinic.) Open square, normal male; open circle, normal female; striped square, male with helicoid peripapillary degeneration; diagonal line, deceased; V, examined; arrow, proband.

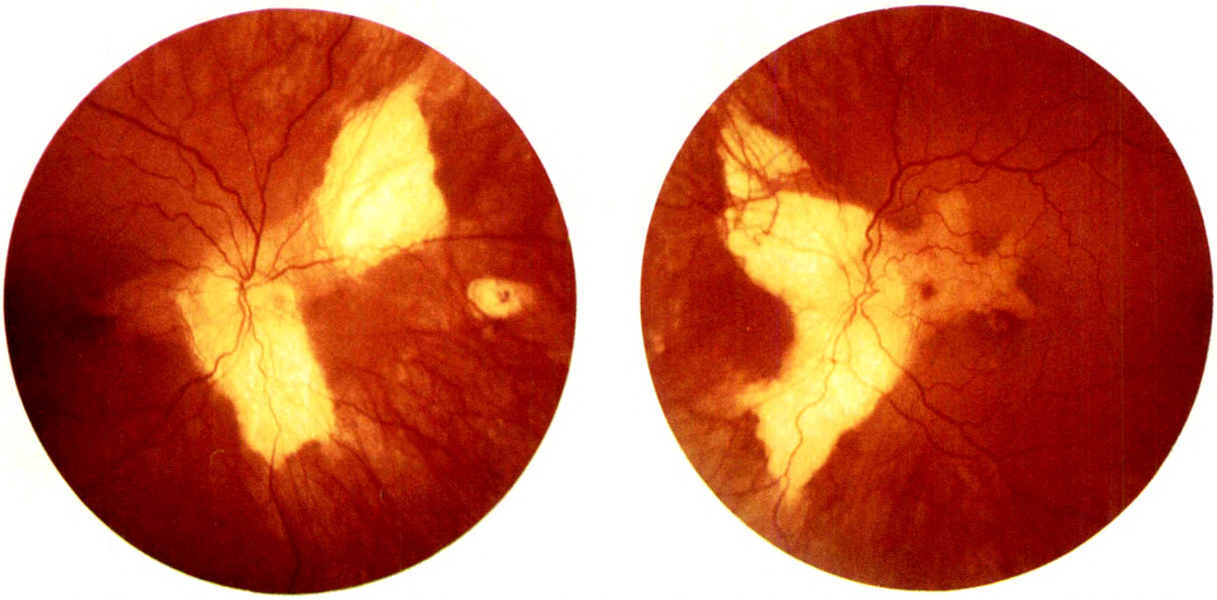


Fig. 3 (Brazitikos and Safran). Patient 2. Both fundi show two wing-shaped dystrophic lesions with their bases at the superonasal and inferonasal margins of the optic disk, directed toward the retinal periphery. An irregular triangular lesion, in which the choroid is not atrophic, is present in the temporal juxtapapillary area, involving also the paramacular area. The right eye (left) demonstrates a round, well-delineated chorioretinal dystrophic lesion in the nasal sector of the retina.

Sveinsson described this ocular condition as "chorioiditis areata." He described four patients, two of whom were a mother and her 4-year-old son.[1] One year later, Rubino described a similar case.[2] The term helicoid peripapillary chorioretinal degeneration was suggested by Franceschetti.[3] Similar cases have been reported in only five studies.[1-5] In 1979, Sveinsson supplemented his first observation and described 13 patients (seven males and six females) in 21 members of the same family in four consecutive generations.[4] Based on both Sveinsson's and our observations, we believe this may be an autosomal dominantly inherited ocular condition. Other cases described in the literature were reported to occur sporadically, although familial studies were not performed.[2,3,5]

Our observation that helicoid peripapillary chorioretinal degeneration is often associated with a mild astigmatism corresponds to Sveinsson's[4] observations. The visual prognosis depends on the severity of the eventual macular involvement. Macular involvement generally increases with age because of a chronic slow progression of the atrophic areas.[4,5]

The differential diagnosis includes ocular disorders causing atrophy of the retinal pigment epithelium and choroid adjacent to the optic disk. Disorders of degenerative or dystrophic origin include malignant myopia, angioid streaks, paravenous retinochoroidal atrophy, and annular pigmentary dystrophy.[6,7] The differential diagnosis of the postinflammatory juxtapapillary atrophy includes mainly serpiginous choroiditis. Diagnosis is not difficult when this ocular abnormality is discovered in childhood. When this condition occurs in an adult patient complaining of a progressive decrease in visual acuity, however, it may be confused with serpiginous choroiditis. The presence of inflammatory signs, the asymmetry of the fundus lesions, the jigsaw-puzzle pattern of chorioretinal atrophy, and pigment clumping characterize serpiginous choroiditis.[8] Fluorescein angiography may show leakage at the borders of the lesions in serpiginous choroiditis but not in helicoid peripapillary degeneration, in which an early hypofluorescence, because of the absence of choriocapillaris and a late staining of the degenerative lesions, are observed.[5] Family history and examination also help determine the diagnosis.

Rubino[2] suggested that this disorder originates from a congenital abnormality of the retinal pigment epithelium (circumpapillaris dysgenesia strati pigmenti). Sveinsson[4] proposed that it is a congenital hereditary abnormality resulting from a developmental disorder of the choroid, the retinal pigment epithelium, or the short posterior ciliary arteries.

We hypothesize that progressive tearing and

retraction of the retinal pigment epithelium around the optic disk occur in this condition. We propose that this tearing is the result of dysplastic, probably congenital, abnormalities of the peripapillary retinal pigment epithelium. Dysplastic abnormalities may involve the junctions of the pigment epithelium cells, as well as the glial tissue that surrounds the optic disk, which could be less resistant. The possibility of tearing of the pigment epithelium is suggested by the linear demarcation and the radial peripapillary location of the triangular retinochoroidal lesions as well as by the slight enhancement of pigmentation along the borders of the lesions. This is especially evident in Case 1 (Fig. 1). In Case 2 (Fig. 3), the linear demarcation of the lesions may be less regular because of progressive changes in the borders of the lesion.

Our hypothesis about the process of tearing and retraction of the retinal pigment epithelium, which could result in the pattern of lesions observed in Case 1, is depicted in Figure 4. We suggest that the linear dehiscence started at two locations at the nasal juxtapapillary termination of the retinal pigment epithelium and progressed toward the superonasal and inferonasal retinal periphery (Fig. 4, stage A). Possibly Bruch's membrane was also involved in the tearing, because of the adhesion between retinal pigment epithelium and Bruch's membrane,[9,10] which is attributable to hemidesmosome-like connections.

At the end of the seventh month of gestation, the axial length of the fetal globe is about 15 mm, and it reaches approximately 21.4 mm at the age of 2 to 3 years.[11] Mitosis in the retinal pigment epithelium is limited to the fundus periphery in late fetal life and ceases completely postnatally.[12,13] During this period, the individual cells of the retinal pigment epithelium hypertrophy to cover the large area created by the growth of the globe. It is conceivable, therefore, that the mechanical stretching of the globe may be the precipitating factor for the tearing process in helicoid peripapillary chorioretinal degeneration.

After the retinal pigment epithelium dehiscence started in Patient 1, lateral progressive retraction of the borders of the tear occurred

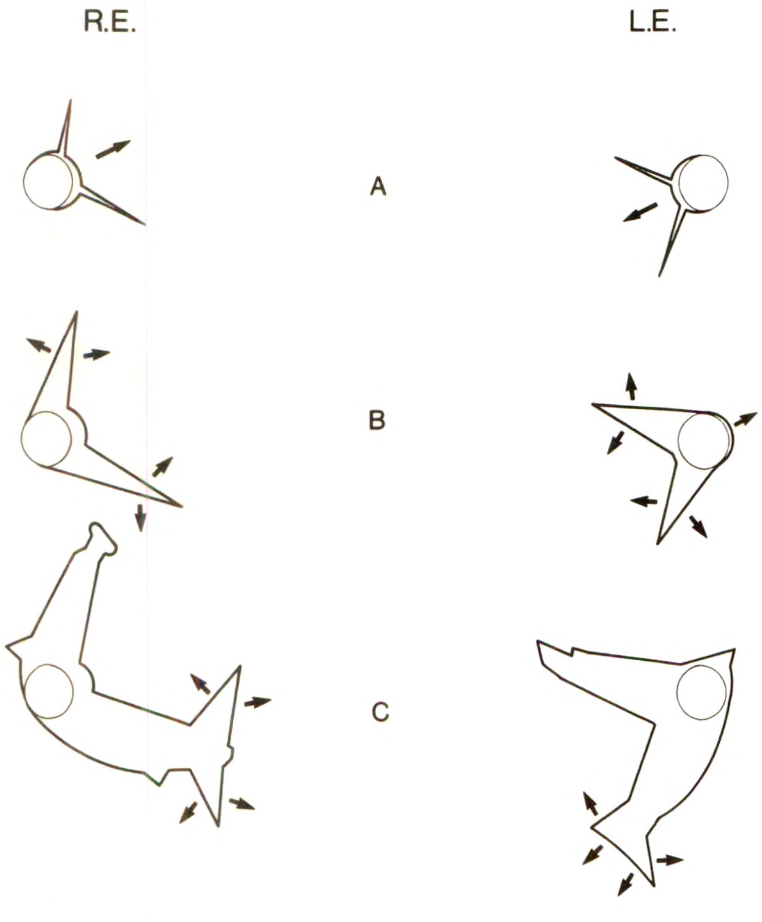


Fig. 4 (Brazitikos and Safran). Stages (A through C) of the suggested retinal pigment epithelium tearing process resulting in the dystrophic wing-shaped lesions observed in Patient 1 (Fig. 1). Oval closed tracings, optic disk borders; bold tracings, retinal pigment epithelium tears. Arrows indicate the direction of retraction.

(Fig. 4, stage B). During this stage, the underlying choriocapillaris either failed to develop or underwent secondary atrophy, because its differentiation depends on pigment epithelium integrity.[14] Eventually, the tearing of the retinal pigment epithelium and the secondary retraction progressed, and smaller lateral tears occurred (Fig. 4, stage C).

Nontraumatic tearing of the retinal pigment epithelium has been recently recognized as a complication of retinal pigment epithelium detachment associated with age-related macular degeneration.[15-17] A few cases of retinal pigment epithelium tearing have also been reported with retinal detachment, chorioretinal scars, and presumed ocular histoplasmosis syndrome.[18,19] Additionally, it has been suggested that tearing of the retinal pigment epithelium–Bruch's membrane complex is involved in the development of lacquer cracks in pathologic myopia as well as in the pathogenesis of angioid streaks.[20,21] In our patients, there was no clinical evidence of pathologic myopia or of systemic conditions most commonly associated with angioid streaks, such as pseudoxanthoma elasticum, Paget's disease of bone, sickle hemoglobinopathy, or acromegaly.[21]

In the presumed tearing of retinal pigment epithelium in helicoid peripapillary degeneration, the retracted margins of the tears do not show the folding or elevation as observed in instances of tearing occurring with detachment of retinal pigment epithelium. Rather, the tears resemble the lacquer cracks of pathologic myopia, in which the mechanical stretching and rupture of the pigment epithelium–Bruch's membrane–choriocapillaris complex is the probable cause.[20]

The macula may be eventually affected in helicoid peripapillary chorioretinal degeneration.[4,5] The small, slightly depigmented, irregular lesions involving the paramacular area in the fundi of Patient 2 (Fig. 3) might illustrate an early stage of this progression of the dystrophic lesions toward the macula. There is evidence, therefore, that in addition to the sharply delineated dystrophic abnormalities, which are evident in early childhood, a more diffuse abnormality of the retinal pigment epithelium may occur later.

References

1. Sveinsson, K.: Chorioiditis areata. Acta Ophthalmol. 17:73, 1939.
2. Rubino, A.: Su una particolare anomalia bilaterale e simmetrica dello strato pigmentato retinico. Boll. Oculist. 19:318, 1940.
3. Franceschetti, A.: A curious affection of the fundus oculi. Helicoid peripapillary chorioretinal degeneration. Its relation to pigmentary paravenous chorioretinal degeneration. Doc. Ophthalmol. 16:81, 1962.
4. Sveinsson, K.: Helicoidal peripapillary chorioretinal degeneration. Acta Ophthalmol. 57:69, 1979.
5. Babel, J.: Les choroïdopathies géographiques et hélicoïdales. Etude clinique et angiographique. Essai de classification. J. Fr. Ophtalmol. 6:981, 1983.
6. Krill, A. E., and Archer, D.: Classification of the choroidal atrophies. Am. J. Ophthalmol. 72:562, 1971.
7. Gass, J. D. M.: Stereoscopic Atlas of Macular Diseases, ed. 3. St. Louis, C. V. Mosby, 1987, p. 294.
8. ———: Stereoscopic Atlas of Macular Diseases, ed. 3. St. Louis, C. V. Mosby, 1987, p. 142.
9. Miki, H., Bellhorn, M. B., and Henkind, P.: Specializations of the retinochoroidal juncture. Invest. Ophthalmol. Vis. Sci. 14:707, 1975.
10. Hogan, M. J., Alvarado, J. A., and Weddell, J. E.: Histology of the Human Eye. An Atlas and Textbook. Philadelphia, W. B. Saunders, 1971, p. 330.
11. Gordon, R. A., and Donzis, P. B.: Refractive development of the human eye. Arch. Ophthalmol. 103:785, 1985.
12. Jakobiec, F. A.: Ocular Anatomy, Embryology and Teratology. Philadelphia, Harper and Row, 1982, p. 53.
13. Streeten, B. W.: Development of the human retinal pigment epithelium and the posterior segment. Arch. Ophthalmol. 81:383, 1969.
14. Korte, G. E., Repucci, V., and Henkind, P.: RPE destruction causes choriocapillary atrophy. Invest. Ophthalmol. Vis. Sci. 25:1135, 1984.
15. Hoskin, A., Bird, A. C., and Sehmi, K.: Tears of detached retinal pigment epithelium. Br. J. Ophthalmol. 65:417, 1981.
16. Gass, J. D. M.: Pathogenesis of tears of the retinal pigment epithelium. Br. J. Ophthalmol. 68:513, 1984.
17. Krishan, N. R., Chandra, S. R., and Stevens, T. S.: Diagnosis and pathogenesis of retinal pigment epithelial tears. Am. J. Ophthalmol. 100:698, 1985.
18. Swanson, D. E., Kalina, R. E., and Guzak, S. V.: Tears of the retinal pigment epithelium. Occurrence in retinal detachments and a chorioretinal scar. Retina 4:115, 1984.
19. Yeo, J. H., Marcus, S., and Murphy, R. P.: Retinal pigment epithelial tears. Patterns and prognosis. Ophthalmology 95:8, 1988.
20. Klein, R. M., and Green, S.: The development of lacquer cracks in pathologic myopia. Am. J. Ophthalmol. 106:282, 1988.
21. Clarkson, J. G., and Altman, R. D.: Angioid streaks. Surv. Ophthalmol. 26:235, 1982.

Posterior Vitreous Cyst

Robert L. Steinmetz, M.D., Bradley R. Straatsma, M.D., and Melvin L. Rubin, M.D.

We observed two patients who had unilateral posterior vitreous cysts; one patient had been observed for 17 years. Both patients were young females who reported transient, infrequent obscurations of vision that were not disabling. One involved eye was emmetropic, and the other was highly myopic. No other ocular abnormalities were present. In the patient observed for 17 years, the physical characteristics of the posterior vitreous cyst remained unchanged. With this stable clinical course, posterior vitreous cyst that does not visually disable the patient may be managed by periodic observation.

POSTERIOR VITREOUS CYST may cause transient[1] or persistent[2] decrease in visual acuity or visual field defect depending on the cyst location relative to the visual axis. We observed two patients who had unilateral posterior vitreous cyst, one of whom had 17 years of follow-up.

Case Reports

Case 1

A 10-year-old girl with a history of bilateral severe myopia and anisometropic amblyopia in her right eye awoke one morning in October 1986 with a brown spot in the field of vision of her left eye. Subsequently, the patient noted that the spot would intermittently obscure her vision, depending on the position of her head. She was examined at the University of Florida Eye Center in March 1987.

Cycloplegic refraction was −21.00 sphere in the right eye and −17.50 sphere equivalent in the left eye. Visual acuity was R.E.: 20/100 and L.E.: 20/40. Right esotropia of 15 prism diopters was present. Results of external, pupillary, and slit-lamp examinations were normal for both eyes. Intraocular pressure was normal.

In the right eye, a Mittendorf dot was present, and results of the ophthalmoscopic examination were unremarkable. In the left eye, a bilobed posterior vitreous cyst was noted (Fig. 1). Its surface was a speckled brown, and internally it was optically clear. The cyst measured approximately 2 × 2 × 4 mm and moved freely in the posterior vitreous with head movement. Periodic observation was recommended.

Case 2

In 1974, Feman and Straatsma[3] described a 14-year-old girl with a posterior vitreous cyst. We have now followed up this patient for 17 years. At the time of her initial examination in 1972 at the Jules Stein Eye Institute, her chief complaint was of an object floating in the visual field of her left eye for approximately one year. She first noticed this condition a few days after minor head trauma.

The patient had 20/20 visual acuity without correction in each eye. Results of external, motility, pupillary, and slit-lamp examinations of both eyes were normal. Intraocular pressure was normal.

Results of media and fundus examination of the right eye were normal; the left eye was normal except for the posterior vitreous cyst (Fig. 2). The cyst measured approximately 3 × 3 × 5 mm. It had a thin, translucent wall that was crenellated and interspersed with pigment flecks. The cyst appeared brown and opaque with retroillumination but was optically clear with direct illumination. No attachments to adjacent structures were identified.

During the 17-year period of observation, results of the comprehensive ophthalmic examination have not changed; the location, size,

Accepted for publication Nov. 30, 1989.

From the Jules Stein Eye Institute and Department of Ophthalmology, UCLA School of Medicine, Los Angeles, California (Drs. Steinmetz and Straatsma), and the Department of Ophthalmology, University of Florida, College of Medicine, J. Hillis Miller Health Center, Gainesville, Florida (Drs. Steinmetz and Rubin). Dr. Steinmetz held an Abe Meyer Fellowship at the Jules Stein Eye Institute, 1987–1989.

Reprint requests to Bradley R. Straatsma, M.D., University of California, Los Angeles, Jules Stein Eye Institute, 100 Stein Plaza, Los Angeles, CA 90024-7000.

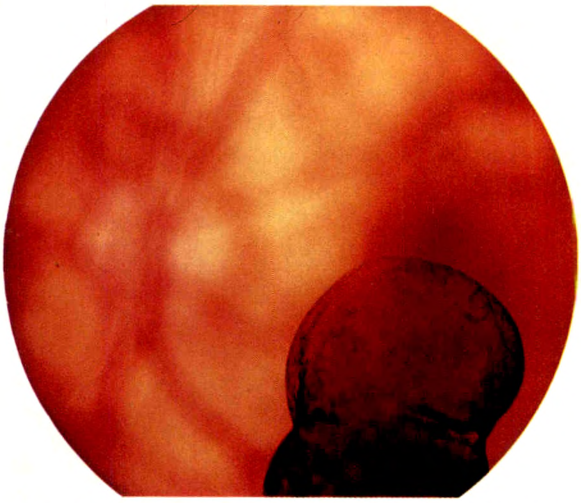


Fig. 1 (Steinmetz, Straatsma, and Rubin). Case 1. Bilobed posterior vitreous cyst.

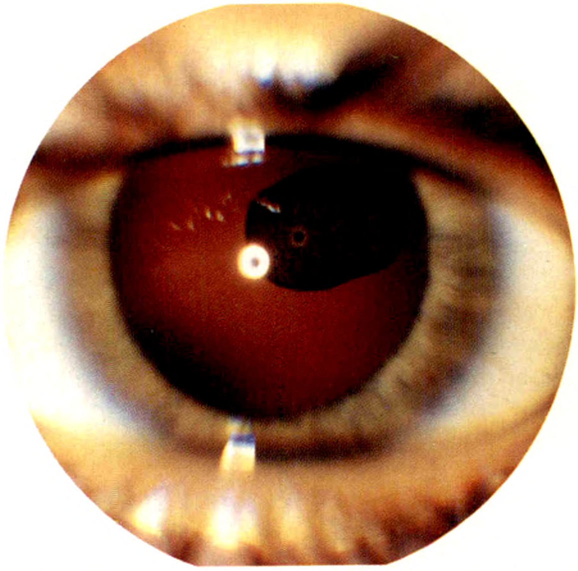


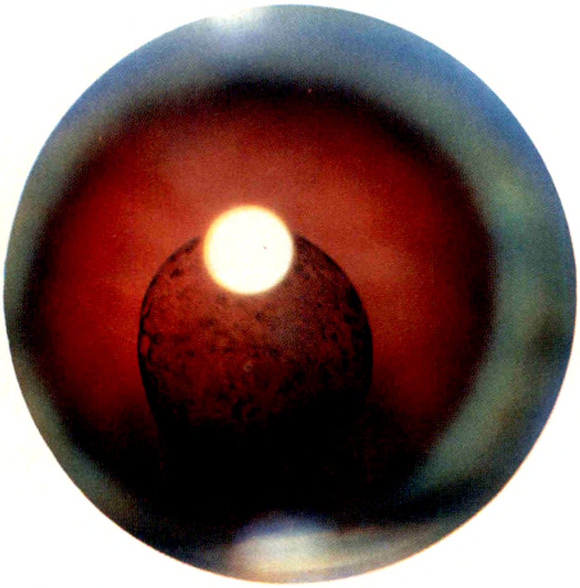
Fig. 2 (Steinmetz, Straatsma, and Rubin). Case 2. Slit-lamp photograph of the posterior vitreous cyst taken in 1972.

and physical characteristics of the cyst have remained the same (Fig. 3). The patient still has infrequent, transient obscurations of her vision, but they are stable and not disabling.

Discussion

Vitreous cysts may generally be seen in one of three circumstances: in eyes that have remnants of the hyaloid system, in eyes with preexistent or coexistent ocular disease, and in eyes that are otherwise normal.

Vitreous cysts in eyes that have remnants of the hyaloid system have been described as small, sessile, pearly-gray structures located on the disk.[4] Alternatively, the cysts can be large, pedunculated, flask-shaped bodies attached to the disk by a stalk. These cysts probably develop from the structures that comprise Bergmeister's papilla, the glial sheath surrounding



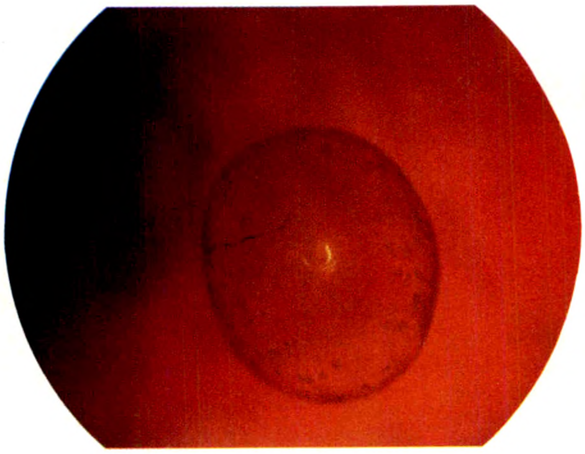


Fig. 3 (Steinmetz, Straatsma, and Rubin). Case 2. Left, Posterior vitreous cyst in 1979. Right, Posterior vitreous cyst in 1988.

the artery, or the associated mesodermal tissue.[4]

Vitreous cysts in eyes with preexisting or coexisting ocular disease have been associated with retinitis pigmentosa,[5,6] inactive central choroidal lesion,[7] retinal detachment, and increasing uveitis.[8] Whether these degenerative or inflammatory conditions participated in the cyst formation is unknown.

Tansley[9] in 1899 was the first to describe a free-floating posterior vitreous cyst in an eye that was otherwise normal. Subsequently, other authors have reported this association.[3,10-12]

Irrespective of the clinical circumstances in which the vitreous cyst is found, the pathogenesis of the posterior vitreous cyst is still unknown. Recently, the cells that lined a vitreous cyst were positively identified. Orellana and associates[2] studied a cyst that was aspirated from the posterior vitreous of a visually symptomatic patient. Light and electron microscopy established that the cells originated from the pigment epithelium. Thus it seems unlikely that this category of vitreous cyst is a remnant of the hyaloid artery system.

Patients with posterior vitreous cyst may be totally asymptomatic[12] or may have a persistent or transient decrease in visual acuity and peripheral field.[1,2] The posterior vitreous cyst may be singular and unilateral,[3] singular and bilateral,[6] or multiple and unilateral.[13] The shape of the posterior vitreous may be spherical,[11] oval,[10] or lobulated,[13] and its surface either smooth or crenellated.[3] The color of the cyst wall ranges from yellow-gray and nonpigmented[6] to brown with irregular pigmentation.[2] The cyst cavity is optically clear.[3] The posterior vitreous cyst may be tethered[5] but usually is free-floating in a localized portion of the vitreous[3] and unattached to the retina or ciliary body.

The temporal relationship between the discovery of the posterior vitreous cyst and recent[11] or remote[2,3] head or ocular trauma has led some authors to consider trauma as the cause of the cyst. Orellana and associates[2] postulated that pigment cells may be dispersed into the vitreous cavity by a preceding ocular disease, such as trauma, inflammation, or degeneration. Wolter, Martonyi, and Smith[11] believed that the relationship to trauma was purely coincidental and that the patient may become symptomatic only after trauma shifts the cyst into the visual axis.

The clinical course of the posterior vitreous cyst has not been extensively documented.[12] Follow-up periods of one year[14] and ten years[10] have disclosed no cyst growth. Subjective cyst enlargement has been reported in two patients.[2]

Most posterior vitreous cysts may be managed by observation because patients are either asymptomatic or are only mildly inconvenienced by the cysts' presence. Two patients have had symptomatic cysts treated. Awan[1] was able to rupture a cyst using the argon laser. The cyst debris settled out of the visual axis and disappeared within several weeks. The uncomplicated aspiration of a symptomatic posterior vitreous cyst by means of the pars plana has been reported.[2]

Our 17-year follow-up of a posterior vitreous cyst that has been stable in all its clinical features confirms the benign, static nature of these cysts. Patients who are not visually disabled by posterior vitreous cyst may need no more than periodic observation.

References

1. Awan, K. J.: Biomicroscopy and argon laser photocystotomy of free-floating vitreous cysts. Ophthalmology 92:1710, 1985.
2. Orellana, J., O'Malley, R. E., McPherson, A. R., and Font, R. L.: Pigmented free-floating vitreous cysts in two young adults. Electron microscopic observations. Ophthalmology 92:297, 1985.
3. Feman, S. S., and Straatsma, B. R.: Cyst of the posterior vitreous. Arch. Ophthalmol. 91:328, 1974.
4. Duke-Elder, S.: Anomalies in the vitreous body. In System of Ophthalmology, vol. 3, pt. 2. London, Henry Kimpton, 1964, pp. 763–770.
5. Litinsky, G. A.: Eine bilaterale runde symmetrische Bildung im Glaskorper. Klin. Monatsbl. Augenheilkd. 87:205, 1931.
6. Perera, C. A.: Bilateral cyst of the vitreous. Report of a case. Arch. Ophthalmol. 16:1015, 1936.
7. MacLean, A. L.: Cyst in the vitreous. Am. J. Ophthalmol. 16:51, 1933.
8. Brewerton, E. W.: Cysts in the vitreous. Trans. Ophthalmol. Soc. U.K. 33:93, 1913.
9. Tansley, J. O.: Cyst of the vitreous. Trans. Am. Ophthalmol. Soc. 8:507, 1899.
10. Casady, J. V.: Congenital cyst of the vitreous. Report of a case. Arch. Ophthalmol. 41:734, 1949.
11. Wolter, J. R., Martonyi, C. L., and Smith, C.: A free-floating vitreous cyst in the otherwise normal eye of a young man. J. Pediatr. Ophthalmol. Strabismus 12:243, 1975.
12. Donaldson, D. D., and Hagler, W. S.: Free floating cysts. Arch. Ophthalmol. 78:400, 1967.
13. Awan, K. J.: Multiple free floating vitreous cysts with congenital nystagmus and esotropia. J. Pediatr. Ophthalmol. 12:49, 1975.
14. Bullock, J. D.: Developmental vitreous cysts. Arch. Ophthalmol. 91:83, 1974.

Anatomy of Arteriovenous Crossings in Branch Retinal Vein Occlusion

David Weinberg, M.D., David G. Dodwell, M.D., and Steven A. Fern, B.S.

We studied the photographic records of 292 eyes, including 103 eyes with branch retinal vein occlusion, 90 fellow eyes, and 99 control eyes without branch retinal vein occlusion. All arteriovenous crossings within three disk diameters of the optic disk, including the crossings at the sites of branch retinal vein occlusions, were studied. The relative positions of the crossing artery and vein could be determined at 1,939 crossings in all eyes. Crossings at which a vein crossed over an artery were a common finding (22.3% to 33.0% of crossings), but were rare at the crossings where branch retinal vein occlusions were found (2.4%). A greater proportion of arterial overcrossings was found in eyes with branch retinal vein occlusions (77.7%) compared to fellow eyes (70.6%) or control eyes (67.0%). Our data indicate that arterial overcrossings are at relatively higher risk of branch retinal vein occlusion than venous overcrossings, and that the risk of branch vein occlusion in an eye is proportional to the number of arterial overcrossings in the eye.

THE OBSERVATION that branch retinal vein occlusion occurs at arteriovenous intersections was made over 100 years ago by Leber.[1] The associations of branch retinal vein occlusion with systemic hypertension and with the retinal vascular manifestations of hypertension have been documented.[2,3]

The crossing of retinal vessels such that the artery lies over (that is, anterior to or innermost to) the vein is considered the normal anatomic configuration. In 1936, however, Jensen observed that venous overcrossings occur at 30% of all crossings in the retinas of normal eyes.[4] The presence of both types of crossings has been demonstrated histologically.[5]

We have rarely seen a branch retinal vein occlusion at an intersection at which the vein crosses over the artery (Fig. 1). References in published studies to similar occlusions are also rare.[4,6] In one series that specifically addressed the anatomy of the crossings at 25 branch vein occlusions, no venous overcrossings were found at the sites of occlusion.[7] We undertook this study to examine the anatomy of the retinal vessels at the sites of branch vein occlusions and to determine if it differs from the anatomy of other arteriovenous intersections in the same eyes or uninvolved fellow and control eyes.

Material and Methods

The files at the retinal photography laboratories of Northwestern University and the New York Hospital, Cornell University from 1985 to 1988 were reviewed for patients with a diagnosis of branch retinal vein occlusion. Only vein occlusions that occurred within three disk diameters of the edge of the optic disk were studied. Central and hemispheric central retinal vein occlusions were excluded. One hundred and three eyes of 100 patients met these criteria.

Using color transparencies, red-free photographs, and fluorescein angiograms of the involved and fellow eyes, the anatomy (artery over vein or vein over artery) of all photographed arteriovenous crossings within three disk diameters of the edge of the optic disk was studied. Intersections occurring on the surface

Accepted for publication Jan. 5, 1990.

From the Department of Ophthalmology, Northwestern University Medical School, Chicago (Dr. Weinberg), and the Department of Ophthalmology, New York Hospital, Cornell Medical Center, New York (Dr. Dodwell and Mr. Fern). This study was supported in part by an unrestricted grant from Research to Prevent Blindness, Inc.

Reprint requests to David G. Dodwell, M.D., Springfield Eye Center, 301 N. 8th St., Springfield, IL 62701.

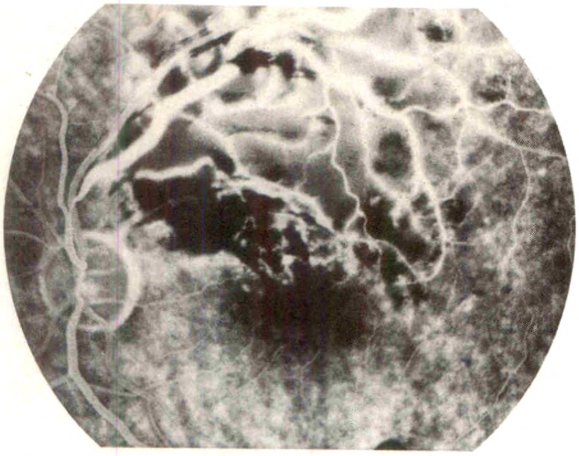


Fig. 1 (Weinberg, Dodwell, and Fern). Example of a branch vein occlusion at a venous overcrossing. Late frame of the angiogram shows staining of the vein as it crosses over the artery.

of the optic disk were excluded. The vessel crossing over was defined as lying innermost or most anterior at the arteriovenous intersection.

At the site of each vein occlusion, the anatomy was designated "artery over vein" or "vein over artery" if the positions of the vessels could be determined with certainty. If the positions of the vessels could not be ascertained, the site was designated "undetermined."

Arteriovenous crossings other than the site of occlusion were designated "artery over vein" or "vein over artery" if the anatomy could be determined with certainty. The number of crossings at which the anatomy could not be determined was not tabulated for these crossings without vein occlusions.

As a control population, the photographic records of 53 consecutive patients referred for fluorescein angiography with diagnoses other than branch retinal vein occlusion were studied. These eyes were analyzed exactly as the fellow eyes of patients with branch retinal vein occlusion.

Statistical testing was performed using chi-square analysis. Statistical significance was defined as $P < .05$, unless otherwise stated.

Results

Age ranged from 21 to 88 years (mean, 66.5 years), and 54 patients were men and 46 were women. The right eye was involved in 53 patients (51.5%), and the left eye was involved in 50 patients (48.5%). Three patients had bilateral branch retinal vein occlusions (two men and one woman). The locations (by quadrant) of the occlusions were as follows: 62 superotemporal (60.2%), 39 inferotemporal (37.9%), one superonasal (1.0%), and one inferonasal (1.0%).

The results are summarized in Figure 2 and the Table. At the site of the branch retinal vein occlusion, the artery lay anterior to the vein in 82 eyes (79.6%). The vein lay anterior to the artery in two eyes (1.9%). In 18 eyes (17.4%), the crossing was undetermined. In one eye (1.0%), the occlusion occurred at an anomalous vein as it exited from the edge of the disk rather than at an arteriovenous crossing. For the 84 vein occlusion sites at which the anatomy could be determined, 82 (97.6%) were arterial overcrossings and two (2.4%) were venous overcrossings.

Determination of the anatomy could not be made in 18 eyes: seven eyes had media opacity, five eyes had hemorrhage, and in six eyes, the intersections were too small to characterize with certainty.

The anatomy of a total of 728 arteriovenous crossings, including the 84 determinable branch vein occlusion sites, was tabulated in the 103

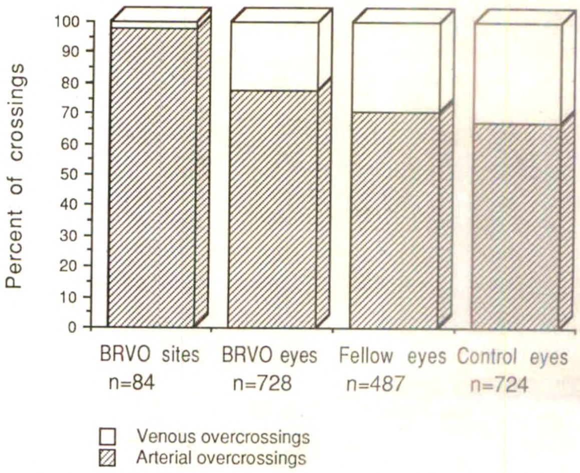


Fig. 2 (Weinberg, Dodwell, and Fern). Distribution of types of arteriovenous crossings among the groups. Unshaded and shaded areas represent percentage of venous and arterial overcrossings, respectively. BRVO sites indicates sites of occlusion in eyes with branch vein occlusion; BRVO eyes, all crossings in eyes with branch vein occlusion; fellow eyes, crossings in fellow eyes of those with branch vein occlusion; control eyes, crossings in eyes of patients without branch vein occlusion; n, the number of arteriovenous crossings at which the positions of the vessels were determined for each group.

TABLE
COMPARISON OF FEATURES OF ARTERIOVENOUS CROSSINGS

	NO. OF EYES	NO. OF CROSSINGS	NO. OF DETERMINABLE CROSSINGS	NO. OF CROSSINGS PER EYE	NO. OF ARTERIAL OVERCROSSINGS (%)	NO. OF VENOUS OVERCROSSINGS (%)
Branch retinal vein occlusion sites	103	102	84	—	82 (97.6)	2 (2.4)
Branch retinal vein occlusion eyes	103	—	728	7.1	566 (77.7)	162 (22.3)
Fellow eyes	90	—	487	5.4	344 (70.6)	143 (29.4)
Control eyes	99	—	724	7.3	485 (67.0)	239 (33.0)

eyes (mean, 7.1 per eye). Of the arteriovenous crossings, 566 (77.7%) were arterial and 162 (22.3%) were venous.

The difference in frequency of arterial and venous overcrossings between the vein occlusion sites and all crossings in the involved eyes was statistically significant (P = .0001).

Of the 103 branch retinal vein occlusions studied, six eyes of three patients had bilateral occlusions and were not included in the analysis of fellow eyes. In another seven cases, photographs of the fellow eyes were unavailable or inadequate for analysis, leaving 90 fellow eyes of 90 patients. Among these eyes, the anatomy of 487 crossings was determined (mean, 5.4 per eye). Fewer crossings per eye were counted in the fellow eyes than in the involved eyes because, in general, fewer photographic frames were available for the fellow eyes. The early frames of the fluorescein angiograms, which were useful for determining the anatomy in the involved eyes, were not available for the fellow eyes.

Of the 487 crossings counted, 344 (70.6%) were arterial overcrossings and 143 (29.4%) were venous overcrossings. Compared to the vein occlusion sites and to the vein occlusion eyes, the differences were statistically significant (P = .0001 and .0063, respectively), with a greater prevalence of venous overcrossings in the fellow eyes.

Of 53 consecutive patients referred for fluorescein angiography with diagnoses other than branch retinal vein occlusion, 99 eyes had photographic records adequate for study. The diagnoses were as follows: diabetes (16), age-related macular degeneration (11), cystoid macular edema (three), optic neuropathy (three), macular hole (three), presumed ocular histoplasmosis (two), myopia (two), macular pucker (two), and other (11). In the last category, no diagnosis was represented more than once. Patient age ranged from 14 to 88 years (mean, 63.9 years), and 22 (41.5%) patients were men and 31 (58.5%) were woman.

The anatomy of 724 crossings was determined in the 99 eyes (mean, 7.3 per eye). Of the crossings, 485 (67.0%) were arterial and 239 (33.0%) were venous overcrossings. The proportion of venous overcrossings in the control eyes was greater than in any other group. This difference was statistically significant compared to the vein occlusion sites (P = .0001) and the vein occlusion eyes (P = .0001), but not compared to the fellow eyes (P = .20).

Discussion

The ages of the patients with branch retinal vein occlusion and the controls were comparable. We would not expect age to be an important variable, because the anatomy of the crossings is determined prenatally and should not influence longevity. The difference in gender between the branch vein occlusion eyes and control eyes was not statistically significant (P = .19). The location of the occlusions was similar to those in previous series,[2,3] with most occlusions in the superotemporal quadrant and most of the remainder in the inferotemporal quadrant. Branch retinal vein occlusions in the nasal quadrants were rare.

Our data confirm the observations of Jensen[4] that venous overcrossings are not a rare finding in normal fundi. Jensen used direct ophthalmoscopy to examine the eyes of 50 normal patients and found venous overcrossings at 30% of all arteriovenous intersections.

Duker and Brown,[7] using color photographs and fluorescein angiograms, found no venous overcrossings at the site of occlusion in their series of 25 branch retinal vein occlusions. For controls, they observed a corresponding crossing in the opposite arcade (superior or inferior)

in the same eye, and all first- and second-order crossings in one eye of 26 patients without branch retinal vein occlusions. The frequencies of venous overcrossings in the two groups were 35% and 32%, respectively.

We used color stereoscopic photographs, red-free photographs, and fluorescein angiograms to examine 292 eyes, and we tabulated 1,939 arteriovenous intersections. We found venous overcrossings at two of 82 vein occlusion sites (2.4%). Venous overcrossings were present in 162 of 728 (22.3%) crossings in involved eyes, in 143 of 487 (29.4%) crossings in fellow eyes, and in 239 of 724 (33.0%) crossings in control eyes.

If branch retinal vein occlusions occur randomly among all crossings, the proportion of venous overcrossings in a series of branch retinal vein occlusions should not differ from their frequency in the fundus overall (between 22% and 35% based on the data of Jensen,[4] Duker and Brown,[7] and ourselves). We found the frequency of venous overcrossings lower and the frequency of arterial overcrossings higher at branch retinal vein occlusion sites than would be predicted based on their overall frequency in the involved eyes, fellow eyes, and control eyes. Thus, arterial overcrossings are at higher risk for branch retinal vein occlusion than venous overcrossings.

The overall frequency of venous overcrossings increased from the involved eyes to the fellow eyes, and from the fellow eyes to the control eyes, with the highest incidence of venous overcrossings (and concomitantly lowest incidence of arterial overcrossings) in the control eyes (Fig. 2). This makes sense statistically, because eyes with a greater frequency of arterial overcrossings have more high-risk crossings, and thus would be expected to have a higher incidence of branch retinal vein occlusion.

Several sources of bias in our data were considered. It is possible that the frequency of venous overcrossings at the site of vein occlusion was underestimated because of an overrepresentation of these crossings in the "undetermined" group. Even if half of the undetermined crossings were venous overcrossings, 91 of 102 occlusions (89.2%) would be arterial overcrossings, and 11 of 102 occlusions (10.8%) would be venous overcrossings. These figures, although they almost certainly overestimate the frequency of venous overcrossings in the "undetermined" group, are still statistically significantly different compared to all other groups (branch retinal vein occlusion eyes, $P = .011$; fellow eyes, $P = .002$; control eyes, $P = .0001$), with a lower frequency of venous overcrossings at sites of branch retinal vein occlusion.

By including the occlusion site in the evaluation of the anatomy of all crossings in the involved eyes, bias may have been introduced, because particular effort was made to characterize these crossings, which had a different frequency distribution. By excluding the 84 determinable occlusion sites from the analysis of crossings in the involved eyes, the proportion of venous overcrossings increases from 22.3% (162 of 728) to 24.8% (160 of 644). This is still less than the proportion in the fellow eyes or the control eyes. The difference remains statistically significant compared to the control eyes ($P = .0011$), but not compared to fellow eyes ($P = .10$).

Differences in the adequacy of the photographic records among the three groups resulted in differences in the mean number of crossings counted per eye. This may have introduced some bias if the locations of the two varieties of crossings are not randomly distributed. For instance, if one type of crossing tends to occur nearer to the disk, or at the intersections of larger vessels, it might be overrepresented in the fellow eyes, because fewer crossings were counted in these eyes, and those that were counted tended to be larger and nearer to the disk. We are unable to determine if such bias exists in our data.

The higher relative risk of branch retinal vein occlusion at arterial overcrossings suggests a hemodynamic difference between arterial and venous overcrossings. We and others[5] have observed that characteristic hypertensive changes seen at arteriovenous crossings are less prominent at venous overcrossings than at arterial overcrossings. Seitz[5] has studied the histologic characteristics of both anatomic variations in normal and hypertensive patients. In the hypertensive patients, there was a thickening of the walls and a narrowing of the lumina of both vessels. At the site of the crossing, the vessels shared a common vascular wall and a common, thickened, adventitial and glial sheath. These changes were independent of which vessel was innermost. In both variants, the course of the artery was unchanged. The vein deviated around the artery, dipping deep into the retina in arterial overcrossings, and bulging against the internal limiting membrane in venous overcrossings. No compression of the underlying vessel was observed. Seitz attributed the more prominent clinical appearance of crossing phe-

nomena (nicking and obscuration of the underlying vessel) in arterial overcrossings to the deeper position of the vein, rather than to any true compression of the vessel.

Thus, by light microscopy, hemodynamic differences between the two anatomic configurations are not obvious. Perhaps there is a difference in the distensibility of the vein lying beneath the artery within the retina in an arterial overcrossing, as opposed to between the internal limiting membrane and the artery in a venous overcrossing. Such physiologic differences could explain the disparity in risk of branch retinal vein occlusion.

References

1. Leber, T.: Die Krankheite der Netzhaut und des sehnerven. In Graefe, A., and Saemisch, T. (eds.): Handbuch der Gesammten Augenheilkunde, Pathologie und Therapie. Leipzig, Verlag Von Wilhelm Engelmann, 1877, pp. 521–535.

2. Gutman, F. A., and Zegarra, H.: The natural course of temporal retinal branch vein occlusion. Trans. Am. Acad. Ophthalmol. Otolaryngol. 78:178, 1974.

3. Blankenship, G. W., and Okun, E.: Retinal tributary vein occlusion. Histology and management by photocoagulation. Arch. Ophthalmol. 89:363, 1973.

4. Jensen, V. A.: Clinical studies of tributary thrombosis in the central retinal vein. Acta Ophthalmol. 1 (suppl. X):1, 1936.

5. Seitz, R. (Blodi, F. C., translator): The "crossing phenomenon." In The Retinal Vessels. St. Louis, C. V. Mosby, 1964, pp. 20–74.

6. Clemett, R. S.: Retinal branch vein occlusion. Changes at the site of obstruction. Br. J. Ophthalmol. 58:548, 1974.

7. Duker, J. S., and Brown, G. C.: Anterior location of the crossing artery in branch retinal vein occlusion. Arch. Ophthalmol. 107:998, 1989.

OPHTHALMIC MINIATURE

"Such a day for cold you never did see, Finn," he said. "I came on a boy with warts standing in the snow. He was frozen to death nearly by the looks of him. His lips were so stiff he couldn't get a word out when I asked him why he didn't come in by the fire with the rest of us. Then I saw the reason plain as day. The cold had had him weeping and his tears had frozen hard clear to the ground. He was tethered there by his two eyes and would have perished surely if I hadn't broken the silver icy streams of his grief with a stick and freed him."

Frederick Buechner, *Brendan*
New York, Atheneum, 1987, p. 12

Tight Scleral Flap Trabeculectomy With Postoperative Laser Suture Lysis

Shlomo Melamed, M.D., Isaac Ashkenazi, M.D., Joseph Glovinski, M.D., and Michael Blumenthal, M.D.

Thirty eyes of 30 patients underwent tight scleral flap trabeculectomy. Of these eyes, 22 underwent laser lysis of the scleral flap sutures, whereas eight eyes did not require such treatment because of low intraocular pressure and active filtering blebs. In the 22 eyes treated, preoperative intraocular pressure was 32.6 ± 8.3 mm Hg, whereas postoperative and prelaser intraocular pressure was 29.3 ± 7.4 mm Hg. Immediately after laser suture lysis, intraocular pressure dropped by 22.7 ± 9.4 mm Hg ($P < .01$) to 6.6 ± 7.0 mm Hg, with elevation of the conjunctival bleb in all eyes treated. After a mean follow-up of 14.4 months, intraocular pressure was controlled (≤ 18 mm Hg) in 20 of the 22 eyes treated (91%). The only major complication was a single case of anterior chamber flattening with intraocular lens touching the corneal endothelium. Combination of tight scleral flap trabeculectomy with subsequent postoperative laser suture lysis is a safe and effective method for low-level intraocular pressure control. This technique seems to combine the advantages of full-thickness filtration and trabeculectomy by achieving relatively low intraocular pressures while minimizing complications caused by excessive aqueous runoff.

FILTERING SURGERY for uncontrolled glaucoma involves the formation of a fistula connecting the anterior chamber and the subconjunctival space, with subsequent effective reduction of intraocular pressure. Two different surgical approaches are currently in use: full-thickness filtration, in which a full-thickness sclerostomy is made, connecting the anterior chamber directly to the subconjunctival space; and trabeculectomy, in which the sclerostomy is performed under a scleral flap, which is later sutured back to its original scleral bed in an attempt to minimize aqueous outflow runoff.

The main advantage of the first technique is the lower intraocular pressure achieved postoperatively.[1-7] Full-thickness filtration, however, is associated with more postoperative complications related to excessive overflow of aqueous, such as anterior chamber flattening, prolonged hypotony, peripheral anterior synechiae, and cataract formation.[1,2,4,7] The advantage of trabeculectomy under the scleral flap is the tamponade effect provided by the dissected and resutured sclera over the sclerostomy, with subsequent reduction of aqueous flow-through. Although this procedure provides short-term postoperative stability, however, final intraocular pressure levels are usually higher than intraocular pressure levels after full-thickness filtration, and long-term success of intraocular pressure control is lower.[6]

In an attempt to benefit from the advantages of both techniques and minimize complications, trabeculectomy with tight closure of the scleral flap was performed in 22 eyes with uncontrolled glaucoma. Postoperatively, the scleral sutures were cut through the conjunctiva using the argon laser. This method, previously described by Savage and associates,[8-10] provides protection from short-term excessive aqueous runoff followed by planned, controlled relaxation of the scleral flap sutures with modification of aqueous flow and reduction of intraocular pressure.

Accepted for publication Nov. 17, 1989.
From the Goldschleger Eye Institute Chaim Sheba Medical Center, Tel-Hashomer, Israel.
Reprint requests to Shlomo Melamed, M.D., Goldschleger Eye Institute, Chaim Sheba Medical Center, Tel-Hashomer 52621, Israel.

Subjects and Methods

Twenty-two eyes of 22 patients with uncontrolled glaucoma underwent argon laser suture

TABLE 1
CHARACTERISTICS OF THE STUDY POPULATION

CHARACTERISTICS	PATIENTS (N = 22) NO.	(%)
Sex		
Male	12	(54.5)
Female	10	(45.5)
Diagnosis		
Primary open-angle glaucoma	10	(45.5)
Pseudoexfoliative glaucoma	4	(18.2)
Angle-closure glaucoma	3	(13.6)
Posttraumatic glaucoma	2	(9.1)
Juvenile glaucoma	2	(9.1)
Low-tension glaucoma	1	(4.5)
Visual field status		
Normal	1	(4.6)
Nasal step	8	(36.4)
Paracentral scotoma	3	(13.6)
Complete Bjerrum scotoma	2	(9.1)
Bjerrum scotoma broken to the periphery	5	(22.7)
Isolated island of vision	3	(13.6)
Glaucoma medications		
One	1	(4.5)
Two	8	(36.4)
Three	6	(27.3)
Four	7	(31.8)
Laser trabeculoplasty	15	(68.2)
Previous ocular surgery		
None	16	(72.7)
Extracapsular cataract extraction and intraocular lens implantation	3	(13.7)
Cyclodialysis	2	(9.1)
Penetrating keratoplasty	1	(4.5)

lysis after tight scleral flap trabeculectomy. The group included 12 men and ten women, and the mean age of the patients was 61.5 years.

Diagnosis of glaucoma subtypes included primary open-angle glaucoma, ten eyes; pseudoexfoliative glaucoma, four eyes; chronic angle-closure glaucoma, three eyes; posttraumatic glaucoma, two eyes; juvenile glaucoma, two eyes; and low-tension glaucoma, one eye (Table 1).

An additional eight eyes underwent tight scleral flap trabeculectomy but did not need postoperative laser suture lysis because of good control of intraocular pressure (10.2 ± 2.3 mm Hg) after trabeculectomy.

The surgical procedure and postoperative care were performed by two of us (S.M. and J.G.). The same surgical steps were followed in all eyes:

1. Retrobulbar anesthesia with 2% lidocaine and 0.5% bupivacaine hydrochloride solutions was used followed by the application of intermittent digital pressure.
2. A fornix-based conjunctival flap was dissected superotemporally or superonasally with meticulous hemostasis of episcleral and bleeding conjunctival vessels.
3. In cases where Tenon's capsule was especially thick, tenonectomy was performed using the Wescott scissors.
4. A 3- to 4-mm equilateral triangular scleral flap was dissected, half scleral thickness in depth, using the diamond knife and a Beaver No. 64 blade.
5. A beveled paracentesis was made with the diamond knife either at the 3:00 or 9:00 o'clock position, and patency was confirmed by the intracameral introduction of Balanced Salt Solution with the 30-gauge cannula.
6. A 2 × 2-mm trabeculectomy was performed under the scleral flap using the diamond knife followed by basal peripheral iridectomy with Vanna's scissors.
7. The scleral flap was closed with three 9/0 nylon sutures one at the apex and one at each side of the triangle. The tightness of these sutures was carefully adjusted to maintain the anterior chamber depth and restrict fluid runoff around the flap edges to little or no flow.
8. The conjunctiva was closed with two 7/0 silk sutures anchored at the corneoscleral limbus at each side. The wound was carefully checked for leakage after the intracameral introduction of Balanced Salt Solution and the application of 2% fluorescein solution.
9. A mixture of betamethasone and gentamicin was injected to the subconjunctiva away from the filtration site.
10. Antibiotic ointment was applied to the cornea, and the eye was patched.

Postoperative treatment included cycloplegic drops twice daily and corticosteroid drops four times daily starting from the first day after surgery. Visual acuity, intraocular pressure measurement, and slit-lamp examination of the anterior chamber and the appearance of the filtration bleb were performed daily for two weeks after surgery. Criteria indicating that the immediate relaxation of the scleral flap sutures was required included an intraocular pressure 18 mm Hg or higher and a flat filtration bleb with a deep anterior chamber. These criteria were believed to indicate high resistance to

aqueous flow through the tightly closed scleral flap. Before laser treatment, gonioscopy was performed to confirm patency of the sclerostomy with no iris, ciliary processes, or fibrin clot occluding its entrance.

For the laser suture lysis procedure, the following steps were taken in all eyes treated:

1. Proparacaine hydrochloride drops were applied to the treated eye.

2. The Hoskins lens[11] was placed against the conjunctiva overlying the scleral flap sutures. Gentle pressure with the lens was usually sufficient to blanch the conjunctival vessels, allowing a direct view of the scleral sutures (Figure). In cases where Tenon's capsule was thick or the conjunctiva was unusually vascular, and the sutures were obscured, more pressure with the lens usually resulted in better visibility and safe treatment.

3. Argon laser parameters are spot size of 50 μm, exposure time of 0.1 second, and power ranging from 500 to 1000 mW. Special care was taken to focus the laser beam posterior to the conjunctiva to avoid inadvertent burning or perforation.

4. One, two, or three sutures were cut, depending on the immediate response to treatment, extent of bleb elevation, anterior chamber shallowing, and intraocular pressure level.

5. Patients were followed up immediately after laser treatment and daily thereafter until the postoperative course was considered stable. Features examined included visual acuity, intraocular pressure level, filtration bleb appearance, anterior chamber depth by means of ophthalmoscopy, and visual field analysis.

TABLE 2

INTRAOCULAR PRESSURE BEFORE AND AFTER TRABECULECTOMY IN 30 EYES

INTRAOCULAR PRESSURE (MM HG)	MEAN	S.D.	RANGE
Preoperative	31.4	7.9	20–48
Postoperative	21.4	12.7	2–45

Results

Twenty-two of 30 eyes underwent laser suture cutting through the conjunctiva after a tight scleral flap trabeculectomy. Preoperative intraocular pressure was 31.4 ± 7.9 mm Hg, whereas the intraocular pressure after surgery was 21.4 ± 12.7 mm Hg, a mean drop of 10.0 mm Hg (Table 2). If only the 22 eyes treated are analyzed, however, the mean preoperative intraocular pressure was 32.6 ± 8.3 mm Hg, and intraocular pressure one day after trabeculectomy was 29.3 ± 7.4 mm Hg. In eight of 30 eyes operated on, the mean intraocular pressure dropped to 10.2 ± 4.9 mm Hg, and these eyes did not undergo laser suture lysis. After laser suture lysis in the 22 eyes, intraocular pressure

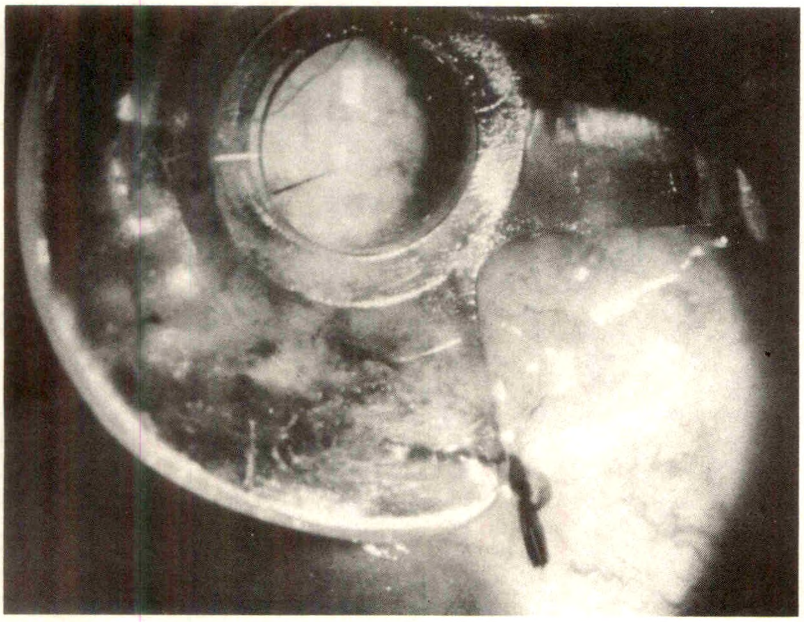


Figure (Melamed and associates). One of the scleral flap sutures seen through the Hoskins lens before laser treatment.

TABLE 3
INTRAOCULAR PRESSURE BEFORE AND AFTER LASER SUTURE LYSIS IN 22 EYES

INTRAOCULAR PRESSURE (MM HG)	MEAN	S.D.	RANGE
Preoperative	32.6	8.3	20–48
Before laser	29.3	7.4	18–45
After laser	6.6	7.0	1–27
Last visit	14.2	5.8	8–34

dropped to 6.6 ± 7.0 mm Hg within one hour after treatment, which is a mean drop of 22.7 ± 9.4 mm Hg ($P < .01$) (Table 3). At the last visit, the mean intraocular pressure was 14.2 ± 5.8 mm Hg after a mean follow-up of 14.4 months (range, four to 24 months). Relevant clinical data after trabeculectomy and laser suture lysis are summarized in Tables 4 to 7.

One day after trabeculectomy, intraocular pressure was greater than or equal to 18 mm Hg in 13 eyes and under 18 mm Hg in 17 eyes. Only two eyes displayed substantial anterior chamber shallowing, both because of conjunctival wound leak. Filtration bleb was flattened in 15 eyes and elevated in 15 eyes (Table 4). Analysis of the 22 eyes before laser suture lysis (Table 5) disclosed that all eyes had an intraocular pressure of greater than or equal to 18 mm Hg with deep anterior chamber and flat bleb. Eleven eyes underwent laser treatment one day after surgery (50%), five eyes underwent the procedure two days after surgery (22.7%), and six eyes underwent the procedure three days or more after trabeculectomy (27.3%). One hour after laser suture lysis, intraocular pressure was less than or equal to 18 mm Hg in 20 of 22 eyes treated (90.9%). Filtration bleb was elevated in all eyes treated, and four eyes (18.2%) had substantial shallowing of the anterior chamber to less than two corneal thicknesses axially (Table 6). At the end of the follow-up period, the intraocular pressure was controlled (≤ 18 mm Hg) in 20 eyes (90.9%). Anterior chamber was deep in all eyes, and the bleb was elevated in all eyes, but only 16 eyes had conjunctival microcystic changes. In the two eyes that failed, no such changes could be demonstrated (Table 7). Visual field analysis showed no change attributed to glaucoma from pretrabeculectomy values.

The average interval between trabeculectomy

TABLE 4
CLINICAL RESPONSE ONE DAY AFTER TRABECULECTOMY

	EYES (N = 30)	
CLINICAL FINDINGS	NO.	(%)
Intraocular pressure		
≤18 mm Hg	13	(43.3)
>18 mm Hg	17	(56.7)
Anterior chamber depth		
≤2 corneal thicknesses	2	(6.7)
>2 corneal thicknesses	28	(93.3)
Bleb appearance		
Elevated	15	(50.0)
Flattened	15	(50.0)

TABLE 5
CLINICAL FINDINGS ONE HOUR BEFORE LASER SUTURE LYSIS

	EYES (N = 22)	
CHARACTERISTICS	NO.	(%)
Days postoperatively		
1	11	(50.0)
2	5	(22.7)
≥3	6	(27.3)
Intraocular pressure		
≤18 mm Hg	0	(0.0)
>18 mm Hg	22	(100)
Depth of anterior chamber		
≤2 corneal thicknesses	0	(0.0)
>2 corneal thicknesses	22	(100)
Bleb appearance		
Elevated	0	(0.0)
Flattened	22	(100)

TABLE 6
CLINICAL FINDINGS ONE HOUR AFTER LASER SUTURE LYSIS

	EYES (N = 22)	
	NO.	(%)
Intraocular pressure		
≤18 mm Hg	20	(90.9)
>18 mm Hg	2	(9.1)
Depth of anterior chamber		
≤2 corneal thicknesses	4	(18.2)
>2 corneal thicknesses	18	(81.8)
Bleb appearance		
Elevated	22	(100)
Flattened	0	(0.0)

TABLE 7
LONG-TERM RESULTS

CHARACTERISTICS	EYES (N = 22) NO.	(%)
Intraocular pressure		
≤18 mm Hg	20	(90.9)
>18 mm Hg	2	(9.1)
Depth of anterior chamber		
≤2 corneal thicknesses	0	(0.0)
>2 corneal thicknesses	22	(100)
Bleb appearance		
Elevated	22	(100)
Flattened	0	(0.0)

and laser suture lysis was 2.5 ± 2.7 days (range, one to 13 days). Cutting of the sutures with the argon laser was successful in 21 of 22 eyes. In one eye, we were unable to lyse the sutures even with a laser power of 1,500 mW, probably because of episcleral bleeding absorbing the argon laser energy. In this patient, Nd:YAG laser was used successfully with seven pulses of 1.2 mJ each to open the sutures without complication.

In five eyes (22.7%), lysis of one suture only was sufficient for intraocular pressure control and active bleb formation. Nine (40.9%) and eight (36.4%) eyes had two and three sutures cut respectively for achieving the same goal. The average laser power required for lysis of one suture was 700 mW (range, 500 to 1,000 mW), with applications totaling two per suture.

In 20 eyes, laser treatment was associated with a sharp drop of intraocular pressure within the first hour after treatment. All of these eyes had an elevated filtration bleb, and four (18.2%) responded with shallowing of the anterior chamber, which usually resolved within one to three days.

There was no conjunctival perforation or leak after laser treatment. There was one case of mild subconjunctival bleeding, which resolved spontaneously after two days. One pseudophakic eye responded with excessive shallowing of the anterior chamber with forward dislocation of the intraocular lens and lens-corneal contact. This condition resolved after three days of conservative medical treatment, and no surgical deepening of the anterior chamber was required.

After a mean follow-up of 14.5 months, intraocular pressure was controlled in 20 eyes. Of these eyes, only four required antiglaucoma therapy (20%). All eyes that failed had flat or vascular filtration blebs, whereas among successful eyes, high blebs with microcystic changes were noted in 16 of 20 eyes (80%). Visual acuity improved in two eyes, worsened in five eyes, and remained unchanged in 15 eyes. Documented progression of cataract was detected in the five eyes with worsened vision.

Discussion

The partial-thickness glaucoma filtering procedure, commonly known as trabeculectomy, is currently the most widely used surgical treatment for glaucoma. The procedure, first described by Cairns in 1968,[12] is associated with fewer complications than full-thickness operations, which include complications such as prolonged hypotony, flattening of the anterior chamber, corneal decompensation, peripheral anterior synechiae, and cataract formation.[1,2,4,7,13-16]

The main advantage of the full-thickness filtering procedure, however, is the lower intraocular pressure achieved postoperatively.[1-7] This low intraocular pressure is especially crucial for eyes with advanced glaucoma where the optic nerves are already severely damaged and only intraocular pressure of less than or equal to 15 mm Hg is considered sufficient for preventing further damage. Because achieving these intraocular pressure levels is usually associated with excessive overfiltration of aqueous and short-term complications related to aqueous overflow, this technique has been abandoned by many glaucoma surgeons.

Our study, as well as others,[10,11] suggests that combining the tight scleral flap trabeculectomy and early suture lysis with the laser is advantageous. The 91% success rate with an anterior chamber shallowing rate of only 18% indicates that this method is efficient and relatively safe.

Our results suggest that despite the surgeon's effort to tightly seal the flap with three sutures, the intraocular pressure dropped postoperatively to the low teens (≤ 15 mm Hg) without laser suture lysis in eight eyes. We did not predict which eye would have intraocular pressure reduction.

The release of the apical suture seems to have had the most dramatic effect on both reduction of intraocular pressure and bleb formation. Because we believed during surgery that the

apical suture was the most effective suture in closing the flap, it was chosen to be the first suture to be lysed. In 16 eyes, however, this was not sufficient to effectively lower the intraocular pressure or form a functioning bleb, and two sutures (nine eyes) or three sutures (eight eyes) had to be released. Unlike Savage and associates,[10] we could not demonstrate more hypotony and shallowing of the anterior chamber after the release of the key suture (in our case, the apical suture). We agree, however, that some sutures may contribute more to aqueous flow resistance, depending on the tightness of the suture and the position of scleral flap edges.

One day postoperatively, eight eyes treated with laser developed shallowing of the anterior chamber. Only one eye, however, had lens-corneal contact jeopardizing the corneal endothelium. Eyes treated with laser two days after surgery did not display anterior chamber shallowing, and this lag time may be considered safe. Apparently, proper sealing of the conjunctival flap is already significant two days after surgery. This sealing with the subsequent increase in resistance to aqueous flow is preferred before laser suture lysis, because it minimizes the rate of anterior chamber flattening and risks such as corneal damage, cataract formation, and prolonged hypotony.

To address whether trabeculectomy and laser suture lysis is superior to trabeculectomy or full-thickness filter alone, one must compare success and complications rates. The success of the procedure must be compared with the full-thickness operations, because the goal is to attain low intraocular pressures. If the definition of success is an intraocular pressure of 16 mm Hg or less, the success rate drops only to 81.8% (18 patients), which is still high. If success is defined as an intraocular pressure of 18 mm Hg or less, our success was 91% (20 patients), which is comparable to the success rate of 94% reported two years after full-thickness filtration.[6]

The rate of complications was surprisingly low in our series. Interestingly, there was no conjunctival burning, perforation, or leak after laser suture lysis. Early cutting of sutures was associated with anterior chamber shallowing in four of 11 eyes treated one day posttrabeculectomy with laser suture lysis (36.4%), and flattening with lens-corneal contact in one eye only. Long-term decrease of visual acuity related to cataract progression has been detected in five eyes (22%), which is similar to the rate of cataract progression of 16% after a similar procedure,[10] or 21% described after trabeculectomy,[6] but substantially less than the rate reported after full-thickness filtration (34% to 38%).

The results of our study strongly suggest that tight scleral flap trabeculectomy with subsequent laser suture lysis is a safe and efficient method for controlling intraocular pressure at relatively low levels while minimizing complications associated with aqueous overflow. Sequential release of sutures starting at least two days after surgery will further reduce the rate of anterior chamber flattening and other related complications.

References

1. Watson, P.: Trabeculectomy. Trans. Ophthalmol. Soc. U.K. 89:523, 1969.
2. Drance, S. M., and Vargas, E.: Trabeculectomy and thermosclerectomy. A comparison of two procedures. Can. J. Ophthalmol. 8:413, 1973.
3. Spaeth, G. L., Joseph, N. H., and Fernandes, E.: Trabeculectomy. A reevaluation after three years and a comparison with Scheie's procedure. Trans. Am. Acad. Ophthalmol. Otolaryngol. 79:349, 1975.
4. Blondeau, P., and Phelps, C. D.: Trabeculectomy vs thermosclerostomy. A randomized prospective clinical trial. Arch. Ophthalmol. 99:810, 1981.
5. Simmons, R. J., and Singh, O. S.: Shell tamponade technique in glaucoma surgery. In Cairns, J. E., Drance, S. M., and Hoskins, H. D., Jr. (eds.): Symposium on Glaucoma. Transactions of the New Orleans Academy of Ophthalmology. St. Louis, C. V. Mosby, 1981, pp. 266–279.
6. Lamping, K. A., Bellows, A. R., Hutchinson, B. T., and Afran, S. I.: Long-term evaluation of initial filtration surgery. Ophthalmology 93:91, 1986.
7. Watkins, F. H., Jr., and Brubaker, R. F.: Comparison of partial-thickness and full-thickness filtration procedures in open-angle glaucoma. Am. J. Ophthalmol. 86:756, 1978.
8. Savage, J. A., and Simmons, R. J.: Staged glaucoma filtration surgery with planned early conversion from scleral flap to full-thickness operation using argon laser. Ophthalmic Laser Ther. 1:201, 1986.
9. Simmons, R. J., Savage, J. A., Belcher, C. D., and Thomas, J. V.: Usual and unusual uses of the laser in glaucoma. In Beckman, H., Campbell, D. G., and L'Esperance, F. A., Jr. (eds.): Symposium on the Laser in Ophthalmology and Glaucoma Update. Transactions of the New Orleans Academy of Ophthalmology. St. Louis, C. V. Mosby, 1985, pp. 154–176.
10. Savage, J. A., Condon, G. P., Lytle, R. A., and Simmons, R. J.: Laser suture lysis after trabeculectomy. Ophthalmology 95:1631, 1988.

11. Hoskins, H. D., and Migliazzo, C., Jr.: Management of failing filtering blebs with the argon laser. Ophthalmic Surg. 15:731, 1984.
12. Cairns, J. E.: Trabeculectomy. Preliminary report of a new method. Am. J. Ophthalmol. 66:673, 1968.
13. Drance, S. M., and Bargass, E.: Trabeculectomy and thermosclerostomy. A comparison of two procedures. Can. J. Ophthalmol. 8:413, 1973.
14. Schwartz, P. L., Ackerman, J., Beards, J., Wessely, Z., Goodstein, S., and Ballen, P. H.: Further experience with trabeculectomy. Ann. Ophthalmol. 8:207, 1976.
15. Kietzman, B.: Glaucoma surgery in Nigerian eyes. A five-year study. Ophthalmic Surg. 7:52, 1976.
16. Shields, M. B.: Trabeculectomy vs full-thickness filtering operation for control of glaucoma. Ophthalmic Surg. 11:495, 1980.

Ophthalmic miniature

The Chinese peasant, like the Egyptian, believed in the glow of the cat's eyes at night to ward off evil spirits, but the Chinese carried the Egyptian's fascination with the eyes a step farther. They believed it was possible to tell time this way—that from dawn the pupil in the cat's eye gradually contracted until it became, at noon, a perpendicular hairline. And then, during the afternoon, the hairline's dilation gradually increased until it was bedtime for people and guard time for cats.

Cleveland Amory, *The Cat Who Came for Christmas*
New York, Penguin Books, 1987, p. 86

Glaucoma in Oculo-Dento-Osseous Dysplasia

Elias I. Traboulsi, M.D., and Marshall M. Parks, M.D.

Two patients with oculo-dento-osseous dysplasia developed glaucoma in infancy or early childhood. Aggressive surgical management resulted in the preservation of vision in both patients in at least one eye. A review of published reports disclosed that glaucoma in oculo-dento-osseous dysplasia develops at different ages and is possibly secondary to a variety of mechanisms. Glaucoma is the main cause of visual loss in this syndrome, for which patients otherwise have a good prognosis for life and intellect. Early screening for glaucoma in oculo-dento-osseous dysplasia is mandatory, especially when there are symptoms that suggest high intraocular pressure.

OCULO-DENTO-OSSEOUS DYSPLASIA is a malformation syndrome that involves the hair, face, eyes, teeth, and bones.[1,2] The mode of inheritance is generally autosomal dominant, but a recessive variety probably exists.[3-5] Patients with oculo-dento-osseous dysplasia have a characteristic physiognomy that features a long face with scarce eyebrows, narrow and short palpebral fissures, microcornea or microphthalmia, and a small nose with hypoplastic alae nasae and a prominent columella. The dental enamel is dysplastic, and microdontia or hypodontia may be present.

Skeletal abnormalities are most prominent in the distal parts of the extremities with camptodactyly or syndactyly of the ulnar two or three digits; the toes are short and frequently lack second metatarsals. Other skeletal abnormalities include calvarial hyperostosis, a heavy mandible with an obtuse angle between its body and rami, plump clavicles, thickened ribs, and poorly tubulated long bones. Generalized hair abnormalities are manifested by hypotrichosis, trichorrhexis, and dry lusterless hair including eyebrows and eyelashes. Less common abnormalities include cleft lip or palate or both, conductive hearing loss, hip dislocation, and osteopetrosis. Intellect is generally normal.

Eyelid abnormalities in oculo-dento-osseous dysplasia include telecanthus and epicanthal folds in most patients. Hypotelorism is present in 40% of patients.[6] Convergent strabismus is a frequent finding. The globe may be involved as a whole with microphthalmos and anterior segment dysgenesis, or the abnormalities may be restricted to dysgenesis of the anterior segment with normal ocular size. Axial length measurements may be normal or below normal.[7] Anterior segment dysgenesis may be more severe in the rarer presumed recessive form of oculo-dento-osseous dysplasia.[4] Remnants of the pupillary membrane are frequently present. Cataracts have been reported in two cases.[8,9] Posterior segment abnormalities have included remnants of the hyaloid system[4,9] and increased numbers of retinal vessels at the optic disk.[7]

Different types of glaucoma have been reported in ten patients with oculo-dento-osseous dysplasia.[1,8,10-14] Although glaucoma was postulated to be present in another two cases of oculo-dento-osseous dysplasia,[7] review of these reports showed that in one instance the patient probably had Rieger's syndrome,[15] and in the other case the patient had a previously undescribed syndrome of glaucoma and probable ectodermal dysplasia, but not oculo-dento-osseous dysplasia.[16]

We treated two patients with oculo-dento-osseous dysplasia and infantile or developmental glaucoma.

Case Reports

Case 1

This patient's glaucoma was first diagnosed in her right eye in 1969 at age 5½ years when

Accepted for publication Dec. 21, 1989.

From the Department of Ophthalmology, Children's National Medical Center (Dr. Traboulsi), and George Washington University School of Medicine (Dr. Parks), Washington, D.C.

Reprint requests to Elias I. Traboulsi, M.D., Department of Ophthalmology, Children's National Medical Center, 111 Michigan Ave. N.W., Washington, D.C. 20010.

she had an intraocular pressure of 40 mm Hg, a cup/disk ratio of 0.8, and visual acuity of R.E.: 20/300. She did not respond to medical treatment and underwent a filtering procedure in the right eye; the filtering bleb failed over a few months. Glaucoma was found in her left eye at age 7 years when she was referred to one of us (M.M.P.) for further treatment. Hallerman-Streiff syndrome had been diagnosed.

On examination, we found typical facial features of oculo-dento-osseous dysplasia with hypotrichosis of the scalp hair and eyebrows, small eyes, and hypoplastic alae nasae. She also had syndactyly and clinodactyly of her fourth and fifth digits in both hands. Intraocular pressure was R.E.: 38 mm Hg and L.E.: 33 mm Hg. The right cornea was larger than the left, and there were large breaks in Descemet's membrane in both eyes; both corneas, however, were less than 10 mm in size, with mild scleralization superiorly and inferiorly. There was a failed filtering bleb superiorly in her right eye, and the patient had undergone a peripheral iridectomy. Posterior synechiae were also present in the right eye, in which there were also posterior cortical lens opacities. In the left eye, extensive remnants of the pupillary membrane were present, which bridged the anterior lens surface and the iris collarette in the superior half of the pupil. A retinoscopy disclosed −12.00 diopters in the right eye and −5.00 diopters in the left eye. A goniotomy was performed in the left eye but was difficult because of poor visualization, and it did not result in decrease in the intraocular pressure. A filtering procedure was subsequently performed on the left eye with good control of the intraocular pressure. With the administration of pilocarpine and later of timolol maleate, the intraocular pressure in the left eye remained adequately controlled over the next several years with a visual acuity of 20/30. The drops were subsequently discontinued, and the intraocular pressure in the left eye continued to be in the 12- to 14-mm Hg range until the patient's last visit in 1988. The right eye was enucleated in 1984 because of absolute glaucoma.

Case 2

This patient was first examined at the age of 4 months because her eyes appeared abnormal and crossed since birth. The prenatal, perinatal, and postnatal histories were unremarkable except for difficulties in breast-feeding. There was no apparent weakness of the facial muscles. Facial appearance was typical of oculo-dento-osseous dysplasia (Figure), although a diagnosis of Moebius syndrome had been considered. She had syndactyly of the third, fourth, and fifth fingers in each hand. Ocular examination disclosed central, steady, and maintained fixation in both eyes and an esotropia of 45 prism diopters. There was a myopia of −5.00 diopters in each eye. The cornea measured 8.5 mm in both eyes, and remnants of the pupillary membrane were present in both eyes. Both lenses were clear. Indirect ophthalmoscopy disclosed moderately severe tilting of the left optic disk.

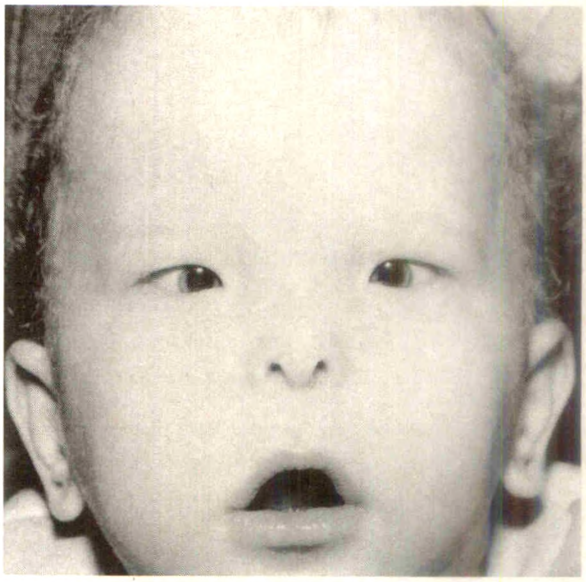


Figure (Traboulsi and Parks). Patient 2 at 8 months of age. Note typical facial features of oculo-dento-osseous dysplasia: narrow eyelid fissures, telecanthus, small nose with prominent columella and receding alae nasae, and fine hair.

At age 6 months, the patient underwent bilateral medial rectus recession by 6 mm, which resulted in an overcorrection to 20 prism diopters of exotropia. Her myopia progressed to −8.00 diopters in both eyes over three months, and photophobia became apparent. Examination under anesthesia at age 9 months showed horizontal breaks in Descemet's membrane in both eyes and increased intraocular pressure (R.E.: 22 mm Hg and L.E.: 29 mm Hg). The gonioscopic appearance of the angle was similar to that in primary infantile glaucoma; the iris was slightly dysplastic with mild hypoplasia inside the collarettes. The cup/disk ratio was 0.5 in the right eye and 0.4 in the left eye. Goniotomies were performed on both eyes four weeks apart with intraocular pressure reduc-

tion to 20 mm Hg in each eye. Timolol maleate 0.5% was started in both eyes. The intraocular pressure increased to 30 mm Hg in the left eye, and a trabeculectomy was performed at age 1½ years with subsequent control of intraocular pressure in that eye.

The patient's myopia continued to progress (−10.50 diopters in the right eye and −13.50 diopters in the left eye) despite good control of intraocular pressure, which was checked under anesthesia on multiple occasions. At age 2½ years, the patient underwent bilateral lateral rectus muscle recession for her consecutive exotropia. She remained orthophoric for several weeks and later varied between moderate esotropia and moderate exotropia on different examinations. She developed amblyopia of her left, more myopic, eye and is currently receiving occlusion therapy. Her visual acuity on her last visit at age 5 years disclosed a visual acuity of R.E.: 20/60 and L.E.: 20/200, and an intraocular pressure of 14 mm Hg in each eye, as measured by applanation tonometry. Her cup/disk ratio had regressed to 0.25 in each eye.

Discussion

Glaucoma can develop in oculo-dento-osseous dysplasia at different ages and has a variety of causes. In infancy, the pathogenesis appears to be similar to that of isolated infantile glaucoma, that is, failure of drainage of aqueous humor because of trabeculodysgenesis.

Trabeculodysgenesis in oculo-dento-osseous dysplasia is probably a manifestation of the anterior segment dysgenesis present in most of these patients. The presence of horizontal breaks in Descemet's membrane in both patients described in this report suggests that their glaucoma began early in infancy. Infantile glaucoma in oculo-dento-osseous dysplasia was previously reported in two patients.[11,13] Anterior segment dysgenesis also predisposes the patient to the development of glaucoma in childhood or early adulthood, as is the case in patients with isolated Axenfeld's-Rieger's spectrum of anomalies. The patients described by Meyer-Schwikerath, Gruterch, and Weyers,[1] Weintraub, Baum, and Pashayan,[14] and Dudgeon and Chisholm[10] are in this second category of glaucoma in oculo-dento-osseous dysplasia. The third category includes patients with an adult-onset, open-angle glaucoma, which was present in one affected member of the family described by Dudgeon and Chisholm.[10] This glaucoma may theoretically also be secondary to anterior segment dysgenesis or it may represent a case of chronic simple glaucoma, which may be more common in patients with oculo-dento-osseous dysplasia. The fourth group includes patients with an angle-closure mechanism, which has been reported by Sugar[11] in one eye of one patient who had infantile glaucoma in the other eye. In that report, Sugar updated the information on a patient he had previously described[12] who also developed angle-closure glaucoma in midadulthood; a lens of normal size in a small globe with a crowded anterior segment is known to predispose an eye to the development of angle-closure glaucoma.

At least three other patients with oculo-dento-osseous dysplasia have been reported to be blind from infancy or early childhood.[8,14] We suspect that glaucoma may have been the cause of blindness in these patients.

Glaucoma is the most common cause of visual loss in patients with oculo-dento-osseous dysplasia. Regular intraocular pressure measurements should be initiated as soon as possible after diagnosis, especially in the presence of symptoms or signs suggesting glaucoma, such as tearing, photophobia, and hazy or enlarged corneas. The management of glaucoma in these patients may be difficult, and initial operations may fail; aggressive management, however, is mandatory and may result in good long-term control of intraocular pressure and the preservation of vision.

References

1. Meyer-Schwikerath, G., Gruterch, E., and Weyers, H.: Mikrophthalmus-syndrome. Klin. Monatsbl. Augenheilkd. 131:18, 1957.
2. Gorlin, R. J., Meskin, L. H., and Geme, J. W.: Oculodentodigital dysplasia. J. Pediatr. 63:69, 1963.
3. Gillespie, F. D.: A hereditary syndrome. "Dysplasia oculodentodigitalis." Arch. Ophthalmol. 71:187, 1964.
4. Traboulsi, E. I., Faris, B. M., and Der Kaloustian, V. M.: Persistent hyperplastic primary vitreous and recessive oculo-dento-osseous dysplasia. Am. J. Med. Genet. 24:95, 1986.
5. International Nomenclature of Constitutional Diseases of Bone. Revision, May 1983. Ann. Radiol. (Paris) 26:457, 1983.

6. Fara, M., and Gorlin, R. J.: The question of hypertelorism in oculodentoosseous dysplasia. Am. J. Med. Genet. 10:101, 1981.

7. Judisch, G. F., Martin-Casals, A., Hanson, J. W., and Olin, W. H.: Oculodentodigital dysplasia. Four new reports and a literature review. Arch. Ophthalmol. 97:878, 1979.

8. Beighton, P., Hamersma, H., and Raad, M.: Oculodentoosseous dysplasia. Heterogeneity or variable expression? Clin. Genet. 16:169, 1979.

9. Guttierez-Diaz, A., Alonso, M. J., and Borda, M.: Oculodentodigital dysplasia. Ophthalmic Paediatr. Genet. 1:227, 1982.

10. Dudgeon, J., and Chisholm, I. A.: Oculo dento digital dysplasia. Trans. Ophthalmol. Soc. U.K. 94:203, 1974.

11. Sugar, H. S.: Oculodentodigital dysplasia syndrome with angle-closure glaucoma. Am. J. Ophthalmol. 86:36, 1978.

12. Sugar, H. S., Thompson, J. P., and Davis, J. D.: The oculo-dento-digital dysplasia syndrome. Am. J. Ophthalmol. 61:1448, 1966.

13. Kadrnka-Lovrencic, M., Jurkovic, S., Reiner-Banovac, Z., Najman, E., and Lovrencic, M.: Dysplasia oculodentodigitalis. Monatsschr. Kinderheilkd. 121:595, 1973.

14. Weintraub, D. M., Baum, J. L., and Pashayan, H. M.: A family with oculodentodigital dysplasia. Cleft Palate J. 12:323, 1975.

15. Brailey, W. A.: Double microphthalmos with defective development of iris, teeth, and anus. Glaucoma at an early age. Trans. Ophthalmol. Soc. U.K. 10:139, 1890.

16. Holmes, L. B., and Walton, D. S.: Hereditary microcornea, glaucoma and absent frontal sinuses. A family study. J. Pediatr 74:968, 1969.

Ophthalmic miniature

Jadine nodded. It seemed like a perfect exit line to her, since she didn't know what he was talking about and didn't want to pursue his thoughts if they were anything like his eyes at this moment. Without melanin, they were all reflection, like mirrors, chamber after chamber, corridor after corridor of mirrors, each one taking its shape from the other and giving it back as its own until the final effect was color where no color existed at all.

Toni Morrison, *Tar Baby*

New York, New American Library, Inc., 1983, p. 62

Blepharoptosis Repair by Fascia Lata Suspension With Direct Tarsal and Frontalis Fixation

Thomas C. Spoor, M.D., and Geoffrey M. Kwitko, M.D.

Nine patients with blepharoptosis and no levator palpebrae superioris muscle function were treated by fixating irradiated fascia lata to the tarsus and frontalis muscles under direct visualization. No recurrences were noted on follow-up, which ranged from four to 24 months. There were no postoperative infections or granuloma reactions. Cosmetically, the height, contour, and symmetry of the eyelid margin and eyelid crease were predictable and satisfactory. This modified method of frontalis suspension may provide a more predictable and cosmetically pleasing result in the treatment of blepharoptosis when minimal or no levator muscle function is present.

SEVERE CONGENITAL or traumatic blepharoptosis with poor to absent levator palpebrae superioris muscle function may be corrected by suspending the eyelid from the brow with fascia lata or suture material.[1,2] This procedure may result in an unacceptable cosmetic appearance and impaired eyelid function.[3] We directly fixed irradiated fascia lata[4] to the tarsus and frontalis muscles through an eyelid crease and eyebrow incision in nine patients who had no levator muscle function. This surgical technique prevents many of the complications associated with the closed methods of using fascia lata and forms a natural eyelid fold.

Patients and Methods

Nine patients, ranging in age from 5 to 82 years, with blepharoptosis and no levator muscle function were operated on. Five patients had congenital blepharoptosis, and four patients lost levator muscle function secondary to trauma (Table). We obtained irradiated fascia lata from the Wills Eye Hospital fascia bank.[4] We encountered no difficulties using irradiated fascia lata.

Surgical technique—Local anesthesia is used in adults, and general anesthesia is used for young children and uncooperative patients. The eyelid and eyebrow are injected subcutaneously along their entire length with 3 to 5 ml of a solution of equal parts of 2% lidocaine with epinephrine (1:200,000) and 0.75% bupivacaine with epinephrine (1:200,000). The patient's upper eyelid crease is marked with a sterile marking pen to match the contralateral upper eyelid. A parallel incision is placed within the eyebrow, measuring 3 to 4 cm horizontally (Fig. 1).

The eyelid crease is incised with a sharp blade along the horizontal length of the upper eyelid. The inferior and superior edges of the skin are grasped with fine-toothed forceps, and the entire tarsus is exposed by sharp dissection. Bleeding is controlled with a bipolar cautery.

The orbital septum is identified and incised with scissors. A plane posterior to the orbital septum and anterior to the levator muscle and fat pads is identified. Fat is excised and cauterized as necessary. The eyebrow is incised with a scalpel and the incision enlarged by spreading with a hemostat until the frontalis muscle is exposed along the entire incision (3 to 4 cm). A curved hemostat is placed in the incision. The orbital septum is penetrated at the arcus marginalis, creating a passage directed toward the eyelid (Fig. 2). The hemostat exits in the eyelid incision just anterior to the levator aponeurosis. This tract is anterior to the levator muscle and posterior to the orbital septum.

Two fascia lata strips are folded in half. The two free ends of each strip are grasped with a hemostat and pulled through the tract connecting the eyelid and eyebrow incisions (Fig. 2).

Accepted for publication Dec. 28, 1989.
From the Kresge Eye Institute of Wayne State University (Dr. Spoor) and Kwitko Eye Center, Montreal, Quebec, Canada (Dr. Kwitko).
Reprint requests to Thomas C. Spoor, M.D., Kresge Eye Institute of Wayne State University, 4717 St. Antoine, Detroit, MI 48201.

TABLE
CHARACTERISTICS OF PATIENTS WITH BLEPHAROPTOSIS AND NO LEVATOR FUNCTION UNDERGOING FASCIA LATA SLINGS

PATIENT NO., SEX, AGE (YRS)	CAUSE OF BLEPHAROPTOSIS	FOLLOW-UP (MOS)	COMMENT
1, F, 45	Congenital	24	2 Previous slings (Supramid and Silastic)
2, F, 10	Congenital	12	Failed Whitnall's sling, failed frontalis suspension
3, M, 10	Congenital	14	Supramid sling as an infant
4, M, 5	Congenital	13	Supramid sling as an infant
5, M, 6	Congenital	8	—
6, M, 33	Trauma	6	—
7, M, 82	Trauma	5	Superior division oculomotor paresis
8, F, 44	Trauma	5	Traumatic extirpation of levator, myositis
9, M, 55	Trauma	4	Anophthalmic socket

The closed loop of each fascia lata strip is placed over the tarsus. The free ends exit the eyebrow incision (Fig. 3). The loops of fascia lata are sutured to the tarsus with multiple alternating 6-0 polyglactin and 5-0 nylon sutures. The most inferior portion of each fascia lata loop is centrally placed on the tarsus to accentuate the eyelid arch (Fig. 4).

The eyelid height and contour are adjusted by pulling the four free ends of fascia lata (Fig. 5). A more refined adjustment is obtained if the patient is sitting. The fascia lata strips are directly fixated to the frontalis muscle using 5-0 polyglactin and 5-0 clear nylon sutures (Fig. 6). The eyelid height and contour are inspected and adjusted as suturing proceeds. Excessive fascia lata is then excised.

The eyebrow incision is approximated with buried 5-0 polyglactin sutures and the skin closed with a 6-0 nylon suture. Excessive skin, orbicularis oculi muscle, and fat are excised from the eyelid incision as required. An eyelid fold is formed by fixating the skin incision to the tarsus (supratarsal fixation) by passing a 7-0 silk suture from the skin to the tarsus to the skin. This maneuver is repeated 5 mm on either side of the first central suture and forms an

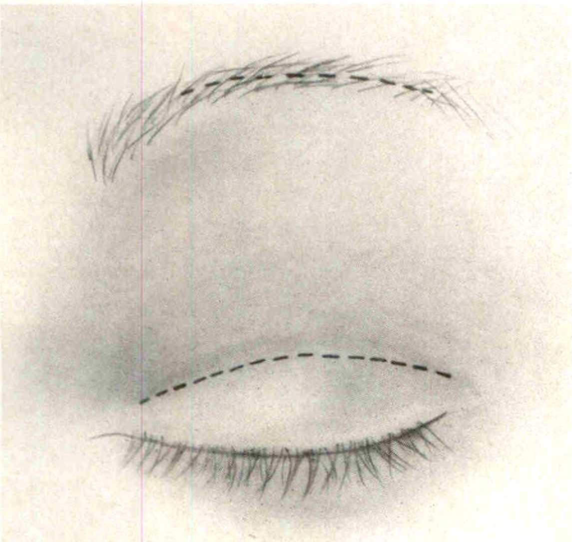


Fig. 1 (Spoor and Kwitko). An eyelid crease and an eyebrow incision are outlined with a sterile marking pen.

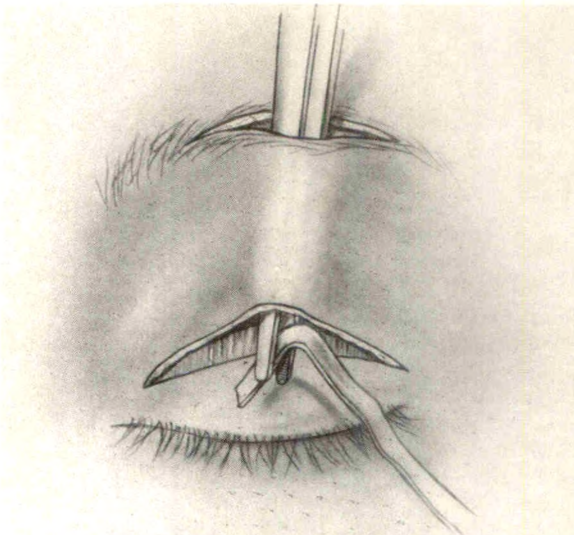


Fig. 2 (Spoor and Kwitko). A fascia lata strip is passed from the eyelid crease incision to the eyebrow incision with a hemostat. The hemostat penetrates the orbital septum at the arcus marginalis and traverses the preaponeurotic space.

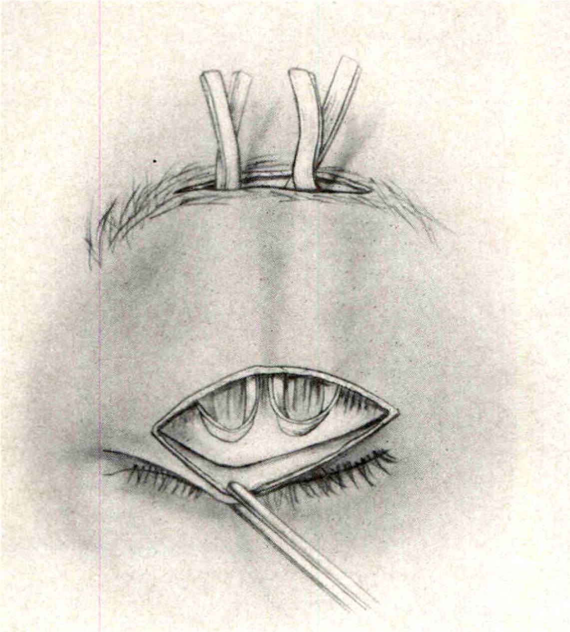


Fig. 3 (Spoor and Kwitko). Two fascia lata strips with loops positioned on the tarsus. Free ends exit the eyebrow incision.

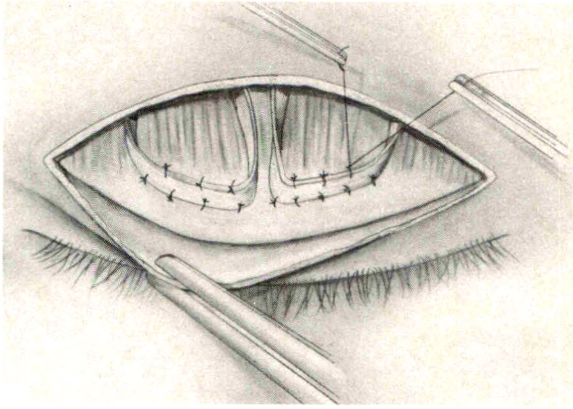


Fig. 4 (Spoor and Kwitko). Fascia lata loops are sutured to the top of the tarsus with interrupted sutures.

eyelid fold. The remaining wound is closed with interrupted 7-0 silk sutures. Topical antibiotic ointment is placed on the eye and over the wounds. The eye is then patched and an iced compress applied. Frost sutures have not been necessary.

Patients are examined the following day for completeness of eyelid closure. Superficial punctate keratopathy, which commonly occurs postoperatively, responds to topical antibiotic drops and ocular lubricants.

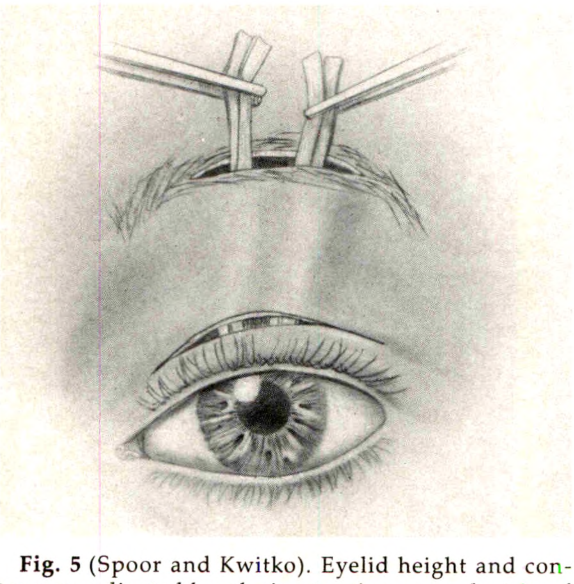


Fig. 5 (Spoor and Kwitko). Eyelid height and contour are adjusted by placing tension on each strip of fascia lata.

Results

Results have been stable over a follow-up period ranging from four to 24 months, and complications have been minimal. Five months after surgery, Patient 8 developed an eyelid abscess that responded to warm compresses and oral antibiotics. Superficial punctate keratopathy, which required copious use of ocular lubricants, was a problem in an 82-year-old man (Patient 7) who underwent cataract extraction three months before blepharoptosis repair. Better eyelid height and contour were obtained in adults operated on under local anesthesia

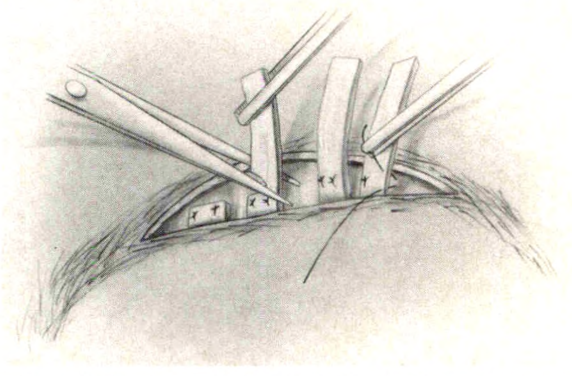


Fig. 6 (Spoor and Kwitko). Fascia lata strips are sutured to the frontalis muscle.

than in children under general anesthesia. As with other blepharoptosis surgery, intraoperative adjustment in the sitting position enhances the surgical result.

Discussion

The advantages of fascia lata over permanent nonabsorbable sutures (less recurrence and granuloma formation) in the treatment of blepharoptosis associated with minimal or no levator muscle function have been described.[4,5] Even with the use of fascia lata, complications occur, including lagophthalmos, undercorrection, eyelid notching, excess postoperative skin, eyelid malpositions (ectropion and entropion), and even globe perforation, orbital hemorrhage, and injury to the superior oblique muscle from passing the Wright needle.[6] Most of these complications result from the method used to place the fascia lata in the eyelid and suspend it from the eyebrow. Blind passage of the large Wright needle, combined with the resistance of the fascia lata passing through the upper eyelid structures, lends itself to technical difficulties and complications. To ensure a permanent or at least a long-lasting blepharoptosis repair, the suspension material must be firmly anchored to both the tarsus and the frontalis muscles.

Modification of the frontalis sling procedure using an eyelid crease incision has been described.[7] Direct frontalis fixation of the suspensory material through an eyebrow incision allows further adjustment of eyelid height and contour and thus gives a more predictable result.

To minimize the cosmetic and functional deformities inherent in the nonphysiologic design of standard frontalis suspension procedures, Patrinely and Anderson[3] advocated obtaining a more physiologic method for elevating the eyelid by passing the fascia lata sling posterior to the orbital septum at the arcus marginalis. Posterior fixation avoids obliteration of the eyelid crease and vertical tension lines, which allows for a more natural arching of the eyelid when the eyebrow is elevated. Difficulty with posterior fixation using a Wright needle prompted the development of a technique for directly fixating the fascia lata to the tarsus and frontalis muscle.

Direct visualization of both the tarsus and the frontalis muscles ensures that the suspensory material is firmly anchored to each and lies deeper in the eyelid. Adjustment of eyelid height and contour is facilitated with this technique and accomplished by pulling and tightening any or all of the four fascia lata strips, extending through the eyebrow incision and fixating these separately (Figs. 5 and 6).

Eyelid margin notching, caused by uneven placement of fascia along the eyelid margin, is avoided in this technique, because the tarsus at the eyelid margin is visualized and the fascia lata can be attached to it, producing a physiologic eyelid margin contour devoid of notching or other malpositions. Once the eyelid is elevated, excessive skin is evident and hangs over the eyelid margin, obliterating the eyelid fold and causing a functional blepharoptosis, although the eyelid margin itself is at an acceptable height. Blepharoplasty is easily performed at the conclusion of this fascia lata slinging procedure. Excessive fat and orbicularis muscle may also be excised. Because the Wright needle is not used, complications associated with its use are avoided.

Direct fixation of the fascia lata to both the tarsus and frontalis muscles allowed us to achieve predictable, adjustable, cosmetically acceptable, and stable results in patients with blepharoptosis and no levator muscle function. Because of our relatively short follow-up period (four to 24 months), we cannot be certain that the long-term results will be as acceptable.

References

1. Payr, E.: Plastik mittles freier Faszientransplantation bei Ptosis. Dtsch. Med. Wochenschr. 35:822, 1909.
2. Wright, W. W.: The use of living sutures in the treatment of ptosis. Arch. Ophthalmol. 51:99, 1922.
3. Patrinely, J. R., and Anderson, R. L.: The septal pulley in frontalis suspension. Arch. Ophthalmol. 104:1707, 1986.
4. Wagner, J. S., Mauriello, J. A., Nelson, L. B., Calhoun, J. H., Flanagan, J. C., and Harley, R. D.: Treatment of congenital ptosis with frontalis suspension. A comparison of suspensory materials. Ophthalmology 91:245, 1984.
5. Crawford, J. S.: Frontalis sling operation. J. Pediatr. Ophthalmol. Strabismus 19:253, 1982.
6. Fox, S. A.: Complications of frontalis sling surgery. Am. J. Ophthalmol. 63:758, 1967.
7. Dortzbach, R. X., and McGetrick, J. J.: Diagnosis and treatment of acquired ptosis. American Academy of Ophthalmology Clinical Module 10. San Francisco, American Academy of Ophthalmology, 1984, p. 6.

A Gas-Permeable Scleral Contact Lens for Visual Rehabilitation

Oliver D. Schein, M.D., Perry Rosenthal, M.D., and Christopher Ducharme

We evaluated the use of a highly gas-permeable, fluid-filled scleral lens for patients with diseased corneas for whom conventional contact lens strategies failed. Fifteen patients were successfully fit with individually fabricated scleral lenses. Significant corneal hypoxia, which limited the use of previous polymethylmethacrylate scleral lenses, was not encountered. Preliminary results suggest that a gas-permeable scleral lens may offer therapeutic as well as visual benefit to some patients with severe corneal disease.

Although the original contact lenses were of a scleral or haptic design, scleral lenses have essentially disappeared from the therapeutic armamentarium in this country. The introduction of polymethylmethacrylate corneal lenses in 1948[1] obviated the need for scleral lenses for the correction of simple refractive disorders, and the use of scleral lenses became limited to a few centers where they were used as therapeutic shells, or for severe ocular surface disorders unresponsive to medical or surgical therapy. There have been essentially two scleral lens types, molded and preformed. Molded lenses are constructed directly from a gel impression of the patient's globe. A polymethylmethacrylate shell is then fashioned from a hard cast taken from the gel. This lens is known as a flush-fitting scleral shell, and its shape follows the contour of the globe. Preformed scleral lenses, made originally from ground glass, and later from polymethylmethacrylate, do not fit the anterior surface of the globe exactly. These lenses and their production have been reviewed by Espy.[2]

The therapeutic potential of scleral lenses in the treatment of patients with diseased corneas has long been recognized; however, application of the lenses has been limited by the epithelial edema and corneal neovascularization that regularly accompany their use. These problems are the consequence of severe corneal hypoxia induced by wearing scleral lenses made of gas-impermeable materials. Molded polymethylmethacrylate lenses have suffered from the same limitations, but may be modified with some success by a variety of gutters and fenestrations to improve the exchange of oxygenated tears.

The use of gas-permeable materials in a scleral design was first described by Ezekiel,[3] who reported the successful rehabilitation of patients with keratoconus, aphakia, severe myopia, and corneal scarring with fenestrated, low-oxygen permeability (16×10^{-11} cm^2 ml O_2/sec ml mm Hg at 36 C) gas-permeable scleral lenses. Significant advances in gas-permeable materials have occurred over the past five years, encouraging further consideration of their application to a scleral design in the rehabilitation of diseased corneas.

Material and Methods

We used a fluoro-silicone/acrylate copolymer (Itafluorofocon B), a rigid material of high oxygen permeability (110×10^{-11} cm^2 ml O_2/sec ml mm Hg at 36 C). A button of this substance is ground to patient specifications using a computer-assisted software design program for lathe fabrication. The basic lens design is shown in Figure 1. It is a meniscus lens consisting of an anterior surface that comprises three curves and a posterior surface that comprises

Accepted for publication Dec. 22, 1989.

From the Cornea Service, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston (Drs. Schein and Rosenthal); Boston Eye Associates, Brookline (Dr. Rosenthal and Mr. Ducharme); and Polymer Technology Corporation, Wilmington (Dr. Rosenthal), Massachusetts.

Reprint requests to Oliver D. Schein, M.D., Massachusetts Eye and Ear Infirmary, 243 Charles St., Boston, MA 02114.

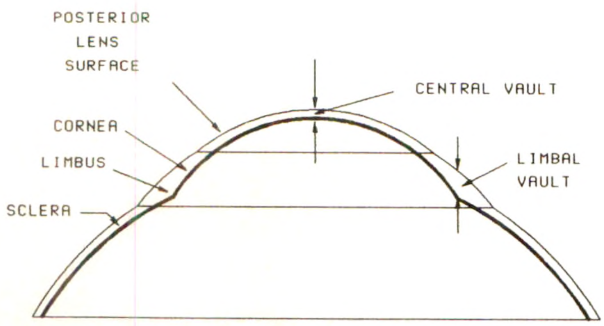


Fig. 1 (Schein, Rosenthal, and Ducharme). Basic gas-permeable scleral contact lens design.

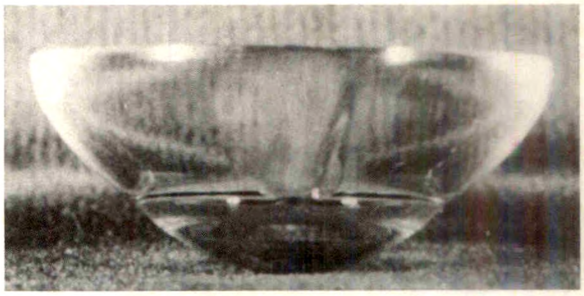


Fig. 2 (Schein, Rosenthal, and Ducharme). Profile view of gas-permeable scleral lens.

three curves. The three primary curves of the posterior surface are, from center outward, the posterior optic, posterior secondary, and the posterior haptic. The haptic portion rests on the sclera and provides the base for the other two curves. The posterior optic curve creates the fluid compartment that acts optically to nullify corneal surface irregularities. The posterior intermediate curve is chosen to clear the limbal area. The radii and optical zones of these two curves together determine the central vault of the lens.

Of the three primary curves of the anterior surface of the lens, the radius of the anterior central curve is chosen according to the dioptric power needed to correct ametropia. The zones of the anterior curves are independent of those of the posterior curves, and their radii are configured to provide minimal lens thickness consistent with optimal lens strength and integrity (approximately 0.50 mm centrally for negative powers). The resultant lens, shown in Figure 2, is filled with nonpreserved isotonic sterile solution at the time of insertion to provide a lacrimal interface. Lens designs are customized to fit the individual eye by evaluating the fitting characteristics of a series of diagnostic scleral lenses of known parameters.

A prospective trial of this lens, approved by the Human Studies Committee of the Massachusetts Eye and Ear Infirmary, is currently underway. Criteria for patient participation include subnormal vision inadequately correctable with spectacles or soft contact lenses, but potentially improvable with rigid contact lenses, and documented intolerance of rigid corneal lenses or fitting failures with rigid or soft lenses because of a distorted anterior segment topography or ocular surface disease. The principal characteristics of all patients fitted to date are shown in the Table.

Case Reports

Case 1

A 48-year-old woman (Patient 10) with neurofibromatosis developed bilateral fifth and seventh cranial nerve palsies after surgery for bilateral acoustic neuromas at age 35 (Fig. 3). After surgery, visual acuity fell to 20/200 in each eye because of corneal neovascularization and a persistent punctate keratitis unresponsive to artificial tears, lubricants, and punctal occlusion. A bandage hydrophilic lens adhered to the dry ocular surface, causing a painful erosion. Bilateral temporal tarsorrhaphies were performed in 1980. These procedures halted the progression of neovascularization but had no beneficial effect on the punctate keratitis or the visual acuity. A gas-permeable scleral lens was fitted after reversing the tarsorrhaphy in the right eye (Fig. 3). Within three weeks, the patient achieved a comfortable wearing time of 16 hours without epithelial edema or increased vascularization. Distance visual acuity with the lens is now 20/40; the patient attains a visual acuity at near of approximately 20/25 with reading glasses, enabling her to read for the first time in over a decade. Corneal protection is achieved during sleep with ocular lubricants and eyelid taping. At the eight-month follow-up examination, early regression of corneal neovascularization was noted.

Case 2

A 35-year-old man (Patient 9) had keratoconus. A penetrating keratoplasty was performed in 1983 in the right eye with resultant 20/25 visual acuity with spectacle correction. Uncorrected visual acuity was L.E.: 20/100 secondary to irregular astigmatism and a hypertrophic superficial scar that is recurrent despite two

TABLE

CLINICAL CHARACTERISTICS OF PATIENTS USING GAS-PERMEABLE SCLERAL LENSES

PATIENT NO., AGE (YRS)	DIAGNOSES AND CONDITIONING	VISUAL ACUITY SPECTACLE-CORRECTED	VISUAL ACUITY SCLERAL LENS	WEARING TIME (HRS)	FOLLOW-UP (MOS)
1, 75	Monocular aphakia	*	20/25	12	46
2, 72	Aphakia, ruptured globe, scleral buckle, 9 diopters astigmatism, superior limbic staphyloma	*	20/30	12	46
3, 19	Marfan's syndrome, bilateral aphakia	20/30 (R.E.) 20/30 (L.E.)	20/25 (R.E.) 20/30 (L.E.)	16	20
4, 55	Keratoconus, after penetrating keratoplasty, 10 diopters astigmatism	20/200	20/50	15	36
5, 29	After penetrating keratoplasty, after wedge resection, 11 diopters astigmatism	20/200	20/20	12	20
6, 24	Keratoconus, apical erosions	20/400	20/40	8	40
7, 46	Keratoconus, corneal scar	20/200	20/70	16	33
8, 46	Severe myopia, keratoconus, fungal keratitis, after penetrating keratoplasty, 8 diopters astigmatism	20/100	20/30	8	31
9, 35	Keratoconus, after superficial keratectomy	20/60	20/25	15	7
10, 53	Neurofibromatosis, bilateral cranial nerve V and VII palsies, tarsorrhaphies both eyes	20/200	20/40	16	8
11, 22	Corneal anesthesia both eyes, fibrovascular pannus both eyes, tarsorrhaphies both eyes	20/800	20/40	12	4
12, 35	Keratoconus, after penetrating keratoplasty, 12 diopters astigmatism	20/200	20/50	8	45
13, 45	Keratoconus, after 2 penetrating keratoplasties, 20 diopters astigmatism	20/800	20/20	8	2
14, 41	Keratoconus, after thermokeratoplasty, after penetrating keratoplasty, 9 diopters astigmatism	20/80	20/25	12	5
15, 43	Keratoconus, after penetrating keratoplasty, after relaxing incision and compression sutures, 8 diopters astigmatism	20/60	20/25	14	7

*Spectacles not feasible because of monocular aphakia.

Fig. 3 (Schein, Rosenthal, and Ducharme). Left, Eye of patient with tarsorrhaphy for combined fifth and seventh cranial nerve palsies, corneal scarring, and diffuse punctate keratitis. Visual acuity, 20/200. Right, Tarsorrhaphy reversed, gas-permeable scleral contact lens in place. Visual acuity, 20/40.

superficial keratectomies (Fig. 4). Repeated efforts to fit the eye with a conventional rigid corneal lens have failed because of discomfort associated with epithelial erosion overlying the hypertrophic scar. A gas-permeable scleral lens was fit to vault the scar. The patient has achieved a comfortable, 15-hour, uninterrupted, daily wearing time and 20/30 visual acuity. There have been no subjective symptoms of erosion or biomicroscopic evidence of epithelial edema.

Case 3

A 55-year-old man (Patient 4) had keratoconus. In 1955, he underwent a 5-mm penetrating keratoplasty in the right eye, and in 1957, he underwent a 7-mm penetrating keratoplasty in the left eye. He now wears a rigid gas-permeable corneal lens in the left eye and has stable 20/25 visual acuity. The right eye has significant corneal astigmatism, which precludes correction with a spectacle lens. The right eye has a potential acuity of 20/50 as measured by hard contact lens overrefraction but has failed numerous contact lens trials with conventional corneal lenses made from polymethylmethacrylate and gas-permeable materials because of lens positioning instability. A piggy-back system (a rigid lens fit over a soft lens) was tried, which was accompanied by an episode of graft rejection and permanent scarring (Fig. 5). A gas-permeable scleral contact lens was fit, vaulting the scarred, elevated

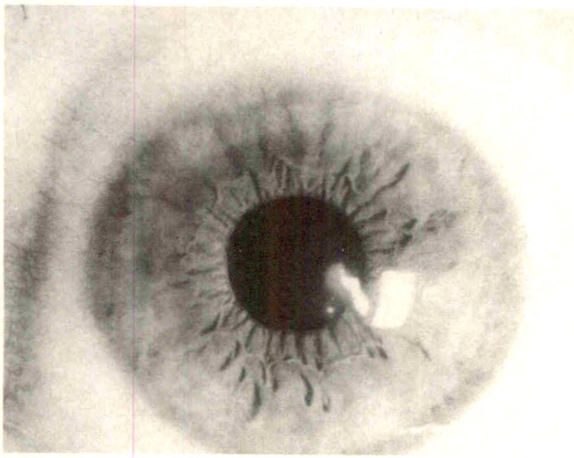


Fig. 4 (Schein, Rosenthal, and Ducharme). Keratoconus with hypertrophic superficial scar preventing comfortable fit with conventional corneal contact lenses.

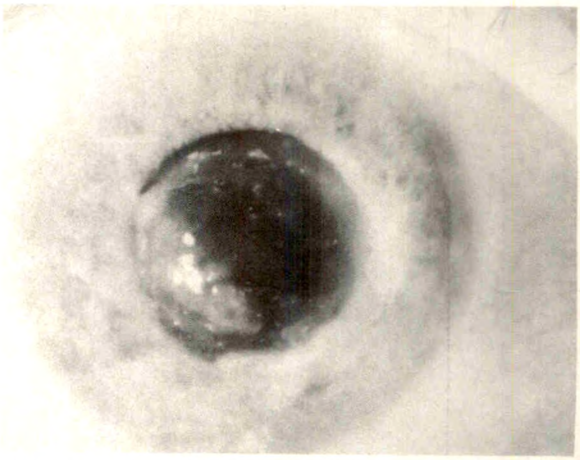


Fig. 5 (Schein, Rosenthal, and Ducharme). Eye of patient with 5-mm corneal graft, irregular astigmatism, and scarring at the graft-host interface.

graft-host interface, permitting a comfortable 15-hour wearing time and visual acuity of 20/50. The corneal graft has been stable over 20 months of observation.

Discussion

Contact lenses play a significant role in the rehabilitation of the diseased ocular surface. The full spectrum of the relevant materials and applications has recently been reviewed by McDermott and Chandler.[4] Yet, there are two major therapeutic problems associated with the use of conventional contact lenses in the visual rehabilitation of patients with corneal disease. The first is visual loss from irregular astigmatism in which the potential acuity as measured by hard contact lens overrefraction cannot be realized because of inability to achieve a stable or comfortable fit. In this category are some patients with keratoconus, cornea plana, marginal degenerations, unusual topographic distortions caused by surgery or other trauma, and the astigmatism and uneven graft-host interface that render corneal lens fitting desirable but problematic after keratoplasty. It may be impossible to fit such patients with conventional contact lenses because their corneal surface cannot tolerate the friction of a corneal rigid lens, or because their anterior segment topography does not allow adequate corneal lens centration or positional stability. The second problem concerns the limitations of therapeutic hydrophilic lenses. Although they can offer symptomatic relief for patients with ocular surface disorders, they offer little visual benefit when there are concomitant topographic distortions. Additionally, they cannot be used reliably in conditions characterized by significant dryness or corneal exposure. Such conditions include keratoconjunctivitis sicca, inactive ocular cicatricial pemphigoid or Stevens-Johnson syndrome, neurotrophic keratitis, and exposure keratitis secondary to structural eyelid defects or neurologic disease.

For a contact lens to be able to overcome the problem of abnormal anterior segment topography and ocular surface disease, it would have to do the following: correct significant amounts of irregular astigmatism; avoid corneal contact in the presence of surface disorders; maintain centration superior to that achievable with corneal lenses; maintain a protective environment; and permit gas exchange adequate to prevent epithelial edema and corneal neovascularization. A gas-permeable scleral contact lens has the potential to meet these criteria. Although the early results are encouraging, the information provided here should be considered preliminary, because the number of patients fit to date is small and the follow-up is limited.

References

1. Heitz, R.: History of contact lenses. In Dabezies, O. H. (ed.): Contact Lenses. The CLAO Guide to Basic Science and Clinical Practice. New York, Grune and Stratton, 1984, ch. 1, pp. 1–19.

2. Espy, J. W.: Scleral lenses and shells. In Dabezies, O. H. (ed.): Contact Lenses. The CLAO Guide to Basic Science and Clinical Practice. New York, Grune and Stratton, 1984, ch. 58, pp. 1–7.

3. Ezekiel, D.: Gas permeable haptic lenses. J. Br. Contact Lens Assoc. 6:158, 1983.

4. McDermott, M. L., and Chandler, J. W.: Therapeutic uses of contact lenses. Surv. Ophthalmol. 33:381, 1989.

Recurrence of Posterior Polymorphous Corneal Dystrophy After Penetrating Keratoplasty

S. Arthur Boruchoff, M.D., Mark J. Weiner, M.D., and Daniel M. Albert, M.D.

Recurrence of a corneal dystrophy after keratoplasty can occur in multiple dystrophies, including macular, granular, and lattice dystrophies. We treated two unrelated patients who had documented posterior polymorphous dystrophy and who, in previously clear grafts, developed haziness in the zone of Descemet's membrane, which led to graft failure. Histologic examination of the keratoplasty specimen showed changes typical of posterior polymorphous dystrophy.

In those corneal dystrophies that result in significant visual impairment, penetrating keratoplasty is successful as a mode of visual rehabilitation. In some of these initially successful corneal grafts, recurrence of the original dystrophy may cause delayed failure of the grafts. This has been reported in granular, lattice, macular, and Reis-Bücklers' dystrophies.[1-4] We treated two unrelated patients in whom posterior polymorphous dystrophy recurred after keratoplasty.

Case Reports

Case 1

A white man, born in 1936, was first examined by us in 1969 because of progressive visual impairment. He had a family history of posterior polymorphous dystrophy; his father, four of his five siblings, and one of his two children had the disease.

Examination disclosed changes typical of widespread posterior polymorphous dystrophy in both eyes, with corneal edema compromising his visual acuity to counting fingers in the left eye. In June 1969, the patient underwent an uncomplicated penetrating keratoplasty in the left eye. The corneal button was examined histopathologically and by electron microscopy. The results of these studies[5] disclosed epithelial-like endothelial cells with numerous microvilli and few microorganelles.

Six months after surgery, the posterior surface of the cornea was noted to have a dull appearance. Several years later, a deep opacity and mild stromal vascularization were observed (Fig. 1). By 1976, the graft had become diffusely cloudy, and a repeat keratoplasty was performed on the left eye. Examination of the corneal button removed at the time of the second keratoplasty showed changes typical of posterior polymorphous dystrophy, with epithelial-like cells present on the posterior corneal surface (Figs. 2 to 4).

Case 2

A white man, born in 1953, had documented posterior polymorphous dystrophy since childhood. His family history disclosed that his father had a similar condition and had undergone penetrating keratoplasty.

By 1978, severe corneal edema had reduced visual acuity in the patient's right eye to counting fingers, and penetrating keratoplasty was performed, improving the visual acuity to 20/40. Clinical examination 1½ years later disclosed faint haze of the endothelium. By 1980, the intraocular pressure in the operated on eye had risen to 38 mm Hg despite maximum medical treatment, and a filtering operation was performed, which successfully controlled the pressure. The lens gradually became cataractous and, in March 1981, an intracapsular cata-

Accepted for publication Dec. 1, 1989.

From the Cornea Service (Drs. Boruchoff and Weiner) and the David G. Cogan Eye Pathology Laboratory (Drs. Weiner and Albert), Massachusetts Eye & Ear Infirmary, and the Department of Ophthalmology, Harvard Medical School, Boston, Massachusetts. This study was supported in part by grant NEI EY01917 (Dr. Albert). Dr. Weiner was a Heed Foundation Fellow (1986–1988).

Reprint requests to S. Arthur Boruchoff, M.D., Cornea Associates, 50 Staniford St., Boston, MA 02114.

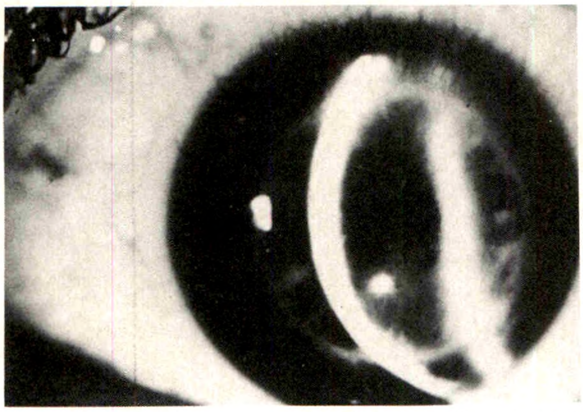


Fig. 1 (Boruchoff, Weiner, and Albert). Case 1. Left eye two years after penetrating keratoplasty. Note marked opacification of the posterior corneal stroma with mild stromal vascularization.

ract extraction was performed; the cornea subsequently became increasingly edematous. In March 1987, a repeat keratoplasty was performed on the right eye. Histologic examination of the excised cornea disclosed the morphologic changes of posterior polymorphous dystrophy (Figs. 5 to 9).

By 1978, visual acuity in the left eye was reduced to 20/200 because of corneal edema. In 1981, penetrating keratoplasty was performed. There has been a progressive diffuse and patchy endothelial haziness (Fig. 10), which is consistent clinically with recurrence of the dystrophy in the graft.

Discussion

Posterior polymorphous dystrophy is clinically characterized by irregularly shaped vacuolar or bullous lesions and patchy haze in the region of Descemet's membrane. The dystrophy is often inherited in an autosomal dominant fashion, although sporadic cases have been described. Typical changes are present from an early age, and the changes may remain stationary or slowly progress. Although the disease is usually bilateral, there may be marked asymmetry in the degree of involvement. In some patients, the dystrophy may be accompanied by peripheral anterior synechiae and glaucoma, making clinical differentiation from iridocorneal-epithelial syndrome difficult.[6-8]

The typical ultrastructural pathologic changes indicative of posterior polymorphous dystrophy from the corneal specimen of Patient 1 were initially described in 1969. There was an abnormal membrane posterior to Descemet's membrane, the posterior surface of which is covered

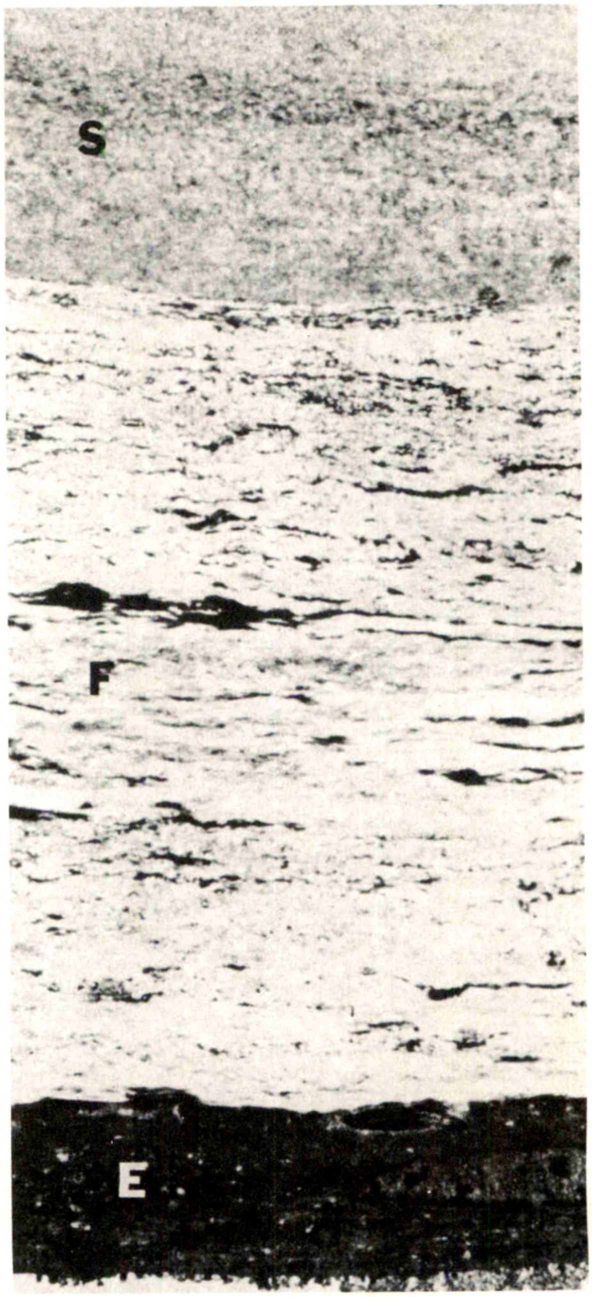


Fig. 2 (Boruchoff, Weiner, and Albert). Case 1. Cross-section of failed corneal graft of the left eye. Note the abnormal fibrous membrane (F) posterior to the corneal stroma (S) and overlying the abnormal epithelial-like cells posteriorly (E) (× 4,000).

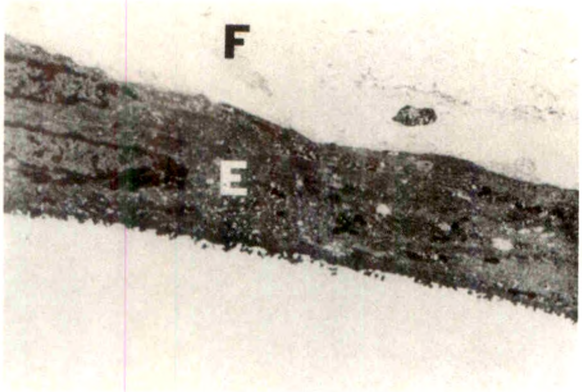


Fig. 3 (Boruchoff, Weiner, and Albert). Case 1. Failed corneal graft of the left eye. The posterior surface is lined by epithelial-like (E) cells, with characteristic numerous microvilli. The epithelial-like cells overlie the abnormal fibrous membrane (F) (×3,500).

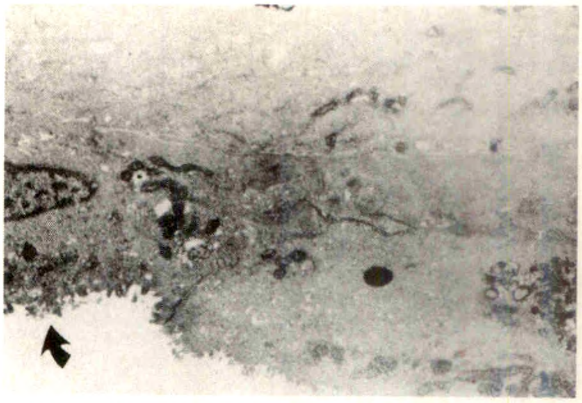


Fig. 4 (Boruchoff, Weiner, and Albert). Case 1. Failed corneal graft of the left eye. Higher magnification of epithelial-like cells shows numerous microvilli (arrow) and scanty microorganelles (× 10,000).

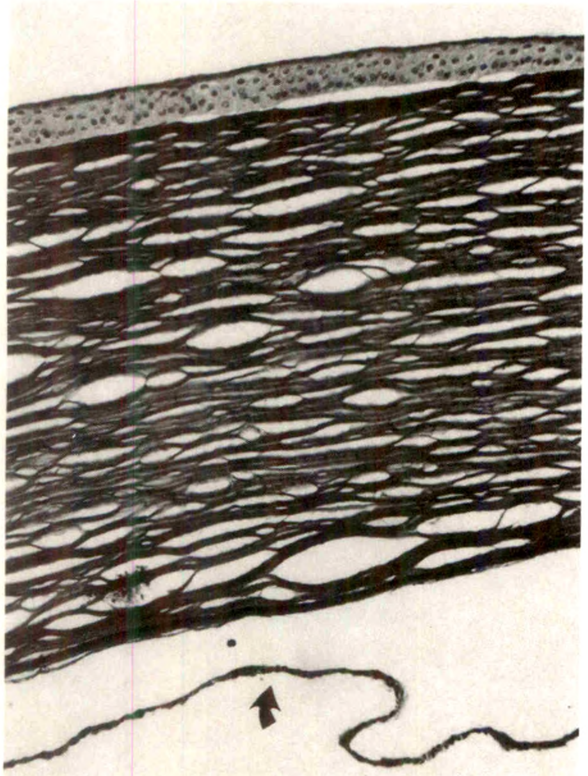


Fig. 5 (Boruchoff, Weiner, and Albert). Case 2. Failed corneal graft of the right eye. Note epithelial edema, stromal scarring, and artifactually detached epithelial-like cells posteriorly (arrow) (hematoxylin and eosin, ×90).

by cells that have the characteristics of epithelium: microvilli, abundant keratofibrils, desmosomes, and sparse microorganelles.

In both of the patients, the initial diagnosis of posterior polymorphous dystrophy was substantiated by typical clinical appearance, family history, and pathologic examination. In each patient, initial graft clarity was followed by a period of progressive endothelial opacification, typified by an unusual haziness of the posterior cornea. Krachmer[9] commented on the puzzling occurrence of retrocorneal membranes in a series of patients after corneal grafting for posterior polymorphous dystrophy. In one patient, he

Fig. 6 (Boruchoff, Weiner, and Albert). Case 2. Failed corneal graft of the right eye. Higher magnification of posterior epithelial-like cells (hematoxylin and eosin, × 200).

Fig. 7 (Boruchoff, Weiner, and Albert). Case 2. Failed corneal graft of the right eye. Posterior portion of the cornea shows Descemet's membrane (DM), with an anterior abnormal fibrous layer (F) and epithelial-like endothelial cells (E), both of which are characteristic of posterior polymorphous dystrophy (× 3,700).

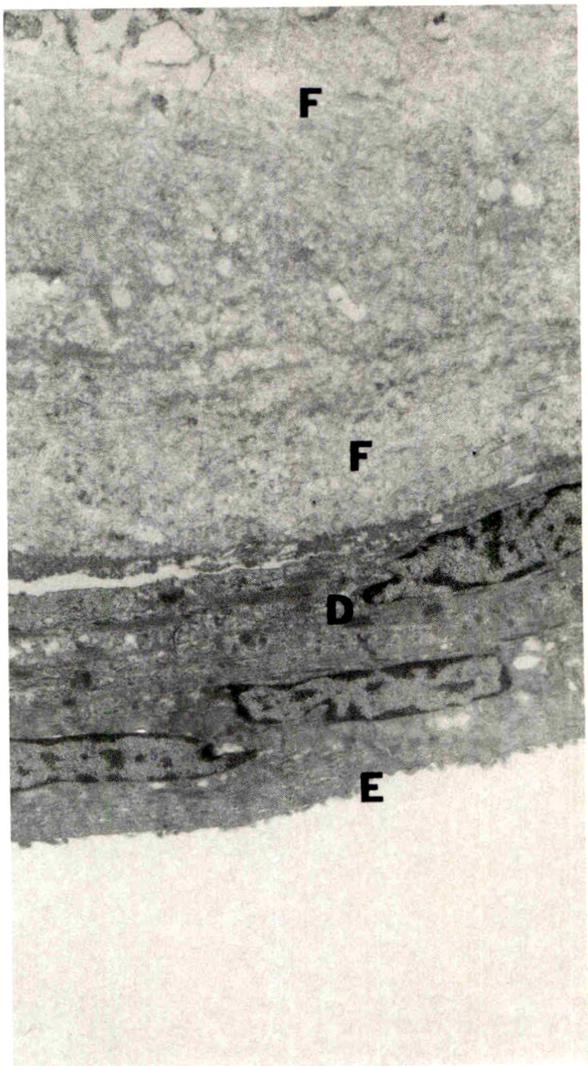


Fig. 8 (Boruchoff, Weiner, and Albert). Case 2. Failed corneal graft of the right eye. Higher magnification of the posterior surface of the cornea shows the abnormal fibrous layer (F) and desmosomes (D) connecting the epithelial-like endothelium (E) here seen forming a multilayer (× 3,650).

postulated that the retrocorneal membranes represented either a form of epithelial downgrowth or a recurrence of the posterior polymorphous dystrophy. Examination of the corneal button disclosed typical epithelial-like cells growing across the posterior surface. Our study supports this finding; Figure 10 shows evidence of this process occurring in vivo. We hypothesize that initially normal and healthy donor endothelium was replaced by abnormal

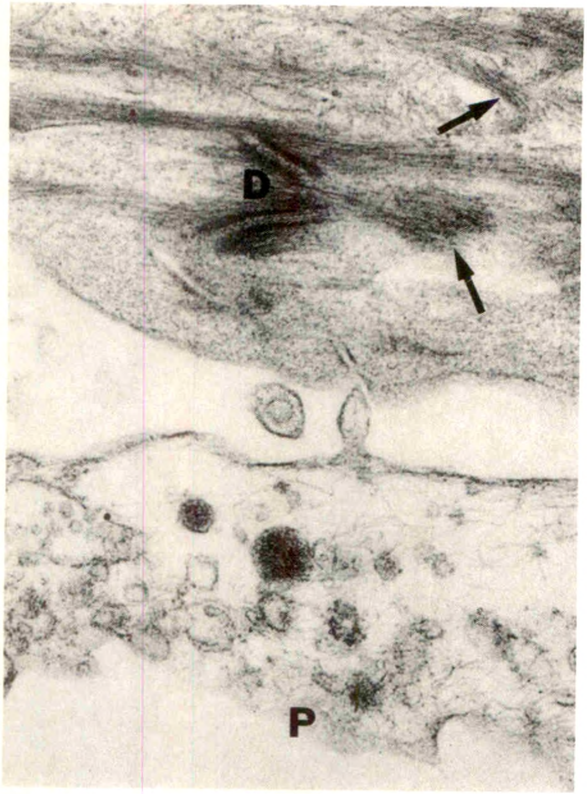


Fig. 9 (Boruchoff, Weiner, and Albert). Case 2. Failed corneal graft of the right eye. Higher magnification of epithelial-like cells shows desmosomes (D) and tonofibrils (arrows). Note degenerated cell processes (P) on the posterior surface (× 40,250).

cells from the periphery of the host cornea. It is possible that abnormal host endothelial cells migrate over the donor endothelial cells, destroying them in the process. Alternatively, donor endothelial cells may be destroyed by some mechanism, such as a rejection phenomenon, and may be then repopulated by migrating host endothelial cells. The origin of the thick fibrous tissue between the Descemet's membrane and the abnormal posterior epithelial-like cells remains a matter of conjecture. It was originally postulated[5] and remains our postulate that the fibrous membrane was elaborated by the aberrant epithelial-like cells. This fibrous tissue is characteristic of posterior polymorphous dystrophy and is present in both the original specimens and in the failed keratoplasty specimens. It has not been found in specimens of epithelial downgrowth. Nor have wound fistula, hypotony, or involvement of the

Fig. 10 (Boruchoff, Weiner, and Albert). Case 2. Corneal graft of the left eye discloses diffuse endothelial haziness consistent with recurrence of the dystrophy in the graft.

iris or ciliary body, all of which are frequently noted in patients with epithelial downgrowth, been noted in either of our patients. Thus, pathologic and clinical evidence suggests that the changes found are not characteristic of epithelial downgrowth, but represent a recurrence of the original dystrophy in the penetrating keratoplasty.

ACKNOWLEDGMENT

For Patient 1, electron microscopy, which resulted in the initial diagnosis of the recurrence of posterior polymorphous dystrophy, was performed by Toichiro Kuwabara, M.D., National Eye Institute, Bethesda, Maryland.

References

1. Stuart, J. C., Mund, M. L., Iwamoto, T., Troutman, R. C., White, H., and DeVoe, A. G.: Recurrent granular corneal dystrophy. Am. J. Ophthalmol. 79:18, 1975.

2. Meisler, D. M., and Fine, M.: Recurrence of the clinical signs of lattice corneal dystrophy (Type 1) in corneal transplants. Am. J. Ophthalmol. 97:210, 1984.

3. Klintworth, G. K., Reed, J., Stainer, G. A., and Binder, P. S.: Recurrence of macular corneal dystrophy within grafts. Am. J. Ophthalmol. 95:60, 1983.

4. Caldwell, D. R.: Postoperative recurrence of Reis-Bücklers' corneal dystrophy. Am. J. Ophthalmol. 85:567, 1978.

5. Boruchoff, S. A., and Kuwabara, T.: Electron

microscopy of posterior polymorphous degeneration. Am. J. Ophthalmol. 72:879, 1971.

6. Waring, G. O., III, Rodrigues, M. M., and Laibson, P. R.: Corneal dystrophies. II. Endothelial dystrophies. Surv. Ophthalmol. 23:147, 1978.

7. Cibis, G. W., Krachmer, J. H., Phelps, C. D., and Weingeist, T. A.: Iridocorneal adhesions in posterior polymorphous dystrophy. Trans. Am. Acad. Ophthalmol. Otolaryngol. 81:OP770, 1976.

8. Quigley, H. A., and Forster, R. F.: Histopathology of cornea and iris in Chandler's syndrome. Arch. Ophthalmol. 96:1878, 1978.

9. Krachmer, J. H.: Posterior polymorphous corneal dystrophy. A disease characterized by epithelial-like endothelial cells which influence management and prognosis. Trans. Am. Ophthalmol. Soc. 83:413, 1985.

OPHTHALMIC MINIATURE

It was her eyes that startled you when you looked at her, because you could see some of the white below the iris, as well as above, and when she blinked—which she did not seem to do as often as most people—the lower lid moved upward as the upper lid moved down, and that is something you rarely see.

Robertson Davies, *The Rebel Angels*
New York, Penguin Books, 1981, p. 17

The Sensitivity of *Neisseria gonorrhoeae, Chlamydia trachomatis,* and Herpes Simplex Type II to Disinfection With Povidone-Iodine

William J. Benevento, B.A., Patrick Murray, Ph.D., Charles A. Reed, A.B., and Jay S. Pepose, M.D.

Povidone-iodine is an effective broad-spectrum disinfectant with no reported toxicity to the cornea and conjunctiva when applied topically in single dose to the ocular surface. We challenged four strains of *Neisseria gonorrhoeae*, a clinical isolate of *Chlamydia trachomatis*, and one strain of herpes simplex virus type II with three different concentrations of povidone-iodine (5%, 1%, and 0.1%) for one minute. The challenge inoculum of *Neisseria gonorrhoeae* and herpes simplex virus type II were completely sterilized by all three solutions. The chlamydia titer was reduced by two log units at the 5% and 1% concentrations, but not the 0.1% concentration. Povidone-iodine may be of potential use in the prophylaxis of newborns against ophthalmia neonatorum.

CREDÉ REPORTED in 1881 that a 2% silver nitrate solution reduced the incidence of gonococcal ophthalmia neonatorum from 10% to 0.3%.[1] Silver nitrate at a concentration of 1% is still used today, though it has been criticized for the chemical conjunctivitis that it engenders[2] and its incomplete protection against chlamydia.[3-6] To avoid these problems, 1% tetracycline or 0.5% erythromycin ointment is frequently substituted for silver nitrate. Though this substitution reduces chemical conjunctivitis, Hammerschlag and associates[6] recently reported that neither tetracycline nor erythromycin is significantly better at preventing chlamydial conjunctivitis in the newborn than silver nitrate. Furthermore, resistance to both tetracycline and erythromycin in *Neisseria gonorrhoeae* has increased significantly in recent years.[7-9]

Chlamydial conjunctivitis is widespread, affecting approximately 0.4% of infants in the United States.[10] Gonococcal ophthalmia neonatorum remains a problem, though a rarer one, affecting 0.04% of neonates.[11] Additionally, there are at least 120 cases per year of viral infections attributable to herpes simplex virus type II,[12] 20% of which include ocular manifestations.[13] These infections occur in spite of prophylaxis with one of the three aforementioned agents. Because of the shortcomings of the current prophylactic regimens, we designed in vitro experiments to evaluate povidone-iodine as a potential alternative method of preventing ophthalmia neonatorum.

Povidone-iodine has been used for many years in ophthalmic surgery and is an effective broad-spectrum disinfectant.[14,15] The solution form is inexpensive, widely available, and has not been associated with corneal or ocular toxicity when applied in a single dose to the intact ocular surface.[16,17] We challenged *Neisseria gonorrhoeae, Chlamydia trachomatis,* and herpes simplex virus type II with povidone-iodine and found it to be an effective disinfective agent against all three pathogens.

Material and Methods

Four strains of *Neisseria gonorrhoeae*, the American Type Culture Collection strain (β lactam −, ATCC 49226), two cervical isolates (β

Accepted for publication Dec. 13, 1989.

From the Departments of Ophthalmology (Mr. Benevento and Dr. Pepose), Pathology (Dr. Pepose), Laboratory Medicine (Dr. Murray), and Pediatrics (Mr. Reed), Washington University School of Medicine, St. Louis, Missouri. This study was supported in part by an unrestricted grant from Research to Prevent Blindness, Inc. Dr. Pepose is the recipient of the American College of Surgeons Faculty Fellowship.

Reprint requests to Jay S. Pepose, M.D., Department of Ophthalmology, Box 8096, Washington University School of Medicine, 660 S. Euclid Ave., St. Louis, MO 63110.

lactam +, stock No. 22619 and β lactam −, stock No. 21038), and a blood isolate (β lactam −, stock No. 20384), were taken from chocolate agar plates and suspended in normal saline at a concentration of approximately 10^8 organisms per milliliter by optical density. In duplicate, 100-μl aliquots of these solutions were inoculated into either normal saline or one of three concentrations of povidone-iodine (Betadine, Purdue Frederick, Norwalk, Connecticut), 5%, 1%, or 0.1% diluted in normal saline. After a one-minute exposure to one of the four solutions, these aliquots underwent two additional log dilutions in normal saline, and 10 μl of each were placed on chocolate agar plates. The solutions were spread with a sterile glass rod, and the plates were placed top-down in a 35 C, 5% CO_2 incubator for 24 hours, at which time the colonies were counted.

A clinical isolate of *Chlamydia trachomatis* from the conjunctiva of a 2-week-old infant was grown in McCoy cells for 72 hours (to maximize elementary bodies) to approximately 5×10^4 inclusion-forming units per milliliter. After a freeze/thaw (−70 C to room temperature) to release the elementary bodies, milliliter aliquots of the solution were exposed to either 5% povidone-iodine, 1% povidone-iodine, or 0.1% povidone-iodine diluted in Earle's minimal essential medium with 10% fetal bovine serum, or minimal essential medium with 10% fetal bovine serum without povidone-iodine. After a one-minute exposure to one of the four solutions, the aliquots underwent a second log dilution in minimal essential medium with 5% fetal bovine serum and were centrifuged onto coverslips containing McCoy cell monolayers in triplicate utilizing the Centers for Disease Control protocol.[18] These solutions were incubated for 30 hours at 36 C, and then the McCoy cell monolayers were stained with a fluorescein-conjugated anti-chlamydia confirmation antibody (Syva, Palo Alto, California). The slides were examined under an ultraviolet microscope, and inclusion bodies were counted.

In preliminary studies, we noted that povidone-iodine was toxic to McCoy cells in concentrations greater than 1%. Sodium thiosulfate, the compound usually employed to inactivate the free iodine component of povidone-iodine, could not be used because it enhanced the toxicity of povidone-iodine to McCoy cells. Thus, a high concentration of chlamydial inclusion-forming units was required during the povidone-iodine challenge to permit subsequent dilution of the povidone-iodine solution to noncytotoxic concentrations before exposure to the McCoy cells.

The Hicks strain of herpes simplex virus type II was diluted to 10^6 plaque-forming units per milliliter. Milliliter aliquots of these solutions were inoculated in triplicate into either Hank's Balanced Salt Solution or 5% povidone-iodine, 1% povidone-iodine, or 0.1% povidone-iodine diluted in Hank's Balanced Salt Solution. After a one-minute exposure to one of the four solutions, these samples underwent two additional log dilutions in minimal essential medium with 5% fetal bovine serum, and 100 μl of each were inoculated onto plates coated with a monolayer of Vero cells with a 2-ml overlay of minimal essential medium with 5% fetal bovine serum. These plates were incubated at 36 C with 5% CO_2 for 90 minutes. At this time, the medium was replaced with an overlay of minimal essential medium with 5% fetal bovine serum with 2% pooled human gamma globulin (Cutter, West Haven, Connecticut) to prevent secondary cell-free viral spread throughout the monolayer. After two days in a 36 C, 5% CO_2 incubator, the overlay was removed, and the cell layer was stained with a 1% solution of crystal violet. The plaques were then counted using a dissecting microscope.

Results

Povidone-iodine was effective in disinfecting the four strains of *Neisseria gonorrhoeae* at the three concentrations tested (Table 1). Approximately 5×10^6 organisms were challenged against each of the povidone-iodine solutions, and no growth was detected in any sample after the one-minute exposure. No differences in the efficacy of disinfection were noted between β-lactamase–positive or β-lactamase–negative isolates of gonococci.

The clinical isolate of chlamydia proved susceptible to povidone-iodine, at the two higher concentrations tested (Table 2). The 5% and 1% povidone-iodine solutions significantly reduced the titer of inclusion-forming units by two log units. No effect was apparent at the 0.1% dilution.

Each challenge of 10^5 plaque-forming units of the Hicks strain of herpes simplex virus type II was effectively neutralized by the three test concentrations of povidone-iodine, with no plaques forming in the Vero cell monolayer (Table 3).

TABLE 1
POVIDONE-IODINE DISINFECTION OF *NEISSERIA GONORRHOEAE*

STRAIN OF *N. GONORRHOEAE*	NO. OF ORGANISMS TESTED (NO POVIDONE)	REDUCTION IN VIABLE ORGANISMS (%) 5% POVIDONE-IODINE	1% POVIDONE-IODINE	0.1% POVIDONE-IODINE
ATCC strain (β lactam −, ATCC 49226)	6.5×10^6	>99.9	>99.9	>99.9
	7.2×10^6	>99.9	>99.9	>99.9
Cervical isolate (β lactam +, stock No. 22619)	7.5×10^6	>99.9	>99.9	>99.9
	6.9×10^6	>99.9	>99.9	>99.9
Cervical isolate (β lactam −, stock No. 21038)	4.0×10^6	>99.9	>99.9	>99.9
	1.9×10^6	>99.9	>99.9	>99.9
Blood isolate (β lactam −, stock No. 20384)	6.9×10^6	>99.9	>99.9	>99.9
	7.2×10^6	>99.9	>99.9	>99.9

Discussion

We demonstrated that povidone-iodine disinfects *Neisseria gonorrhoeae* and herpes simplex virus type II in concentrations as low as 0.1%, and is effective against *Chlamydia trachomatis* in both 5% and 1% dilutions. A previous study of chlamydial inactivation by povidone-iodine found complete microbicidal activity at concentrations as low as 0.025%.[19] The difference in results may stem from the method of assaying chlamydia (culture with immunofluorescence stain vs inoculation into chicken eggs) or the duration of exposure to povidone-iodine (one minute vs 15 minutes). Additionally, we exposed chlamydia to povidone-iodine while in a minimal essential medium with 10% fetal bovine serum solution, which decreases the efficacy of povidone-iodine (unpublished data). Unfortunately, this problem could not be avoided. Povidone-iodine is toxic to McCoy cells in concentrations greater than 1%. Thus, a high concentration of chlamydial inclusion-forming units was needed during the povidone-iodine challenge, allowing for subsequent dilution before exposure to the McCoy cells. Because we could not attain a concentration of chlamydia greater than 5×10^4 inclusion-forming units per milliliter, dilution before the povidone-iodine challenge was impossible. It is therefore probable that chlamydia are more susceptible to povidone-iodine than our data indicate.

Povidone-iodine appears to offer many advantages over currently used prophylactic agents for ophthalmia neonatorum. In a 5% concentration, it is tolerated well in a single topical application[20,21] and offers antiviral activity against herpes simplex virus type I[22] and human immunodeficiency virus[23] in addition to the activity against herpes simplex virus type II that we noted. Two groups of investigators have tried to induce resistance to povidone-iodine in gram-negative species and have failed.[24,25] In 30 years of use, there have been two instances of contamination reported, one with *Pseudomonas aeruginosa*[26] and the other with *Pseudomonas cepacia*.[27,28] In 1982 Berkelman, Holland, and Anderson[29] showed that the *Pseudomonas cepacia* from the contaminated solution was

TABLE 2
POVIDONE-IODINE DISINFECTION OF *CHLAMYDIA TRACHOMATIS*, CONJUNCTIVAL ISOLATE

EXPERIMENT	NO. OF INCLUSION-FORMING UNITS (NO POVIDONE)	REDUCTION IN INCLUSION-FORMING UNITS (%) 5% POVIDONE-IODINE	1% POVIDONE-IODINE	0.1% POVIDONE-IODINE
1	8.2×10^3	98.8	98.8	−20.7
2	5.6×10^4	99.6	99.8	32.4
3	4.4×10^4	99.8	>99.9	86.9

TABLE 3

POVIDONE-IODINE DISINFECTION OF HERPES SIMPLEX VIRUS TYPE II, HICKS STRAIN

EXPERIMENT	NO. OF PLAQUE-FORMING UNITS (NO POVIDONE)	REDUCTION IN PLAQUE-FORMING UNITS (%) 5% POVIDONE-IODINE	1% POVIDONE-IODINE	0.1% POVIDONE-IODINE
1	1.9×10^6	>99.9	>99.9	>99.9
2	1.1×10^6	>99.9	>99.9	>99.9
3	6.7×10^5	>99	>99	>99

actually susceptible to povidone-iodine from the same lot, suggesting mechanical protection by organic or inorganic material.

Until prenatal screening for the pathogens associated with ophthalmia neonatorum is universal, some form of prophylaxis is necessary to prevent this disease, especially in parts of the third world where prenatal screening is difficult and the incidence of maternal infection is high.[30] A clinical trial to evaluate povidone-iodine as a potential prophylactic agent for ophthalmia neonatorum is now indicated.

References

1. Credé, K. S. F.: Die Verhutung der Augenentz Ündung der Neugeborenen. Arch. Gynäkol. 17:50, 1881.

2. Nishida, H., and Risemberg, H. M.: Silver nitrate ophthalmic solution and chemical conjunctivitis. Pediatrics 56:368, 1975.

3. Bell, T. A., Sandström, K. I., Gravett, M. G., Mohan, K., Kuo, C., Stamm, W. E., Eschenbach, D. A., Chandler, J. W., Holmes, K. K., Foy, H. M., and Grayston, J. T.: Comparison of ophthalmic silver nitrate solution and erythromycin ointment for prevention of natally acquired *Chlamydia trachomatis*. Sex. Transm. Dis. 14:195, 1987.

4. Hammerschlag, M. R., Chandler, J. W., Alexander, E. R., English, M., Chiang, W., Koutsky, L., Eschenbach, D. A., and Smith, J. R.: Erythromycin ointment for ocular prophylaxis of neonatal chlamydial infection. JAMA 244:2291, 1980.

5. Laga, M., Plummer, F. A., Piot, P., Datta, P., Namaara, W., Ndinya-Achola, J. O., Nzanze, H., Maitha, G., Ronald, A. R., Pamba, H. O., and Brunham, R. C.: Prophylaxis of gonococcal and chlamydial ophthalmia neonatorum. A comparison of silver nitrate and tetracycline. N. Engl. J. Med. 318:653, 1988.

6. Hammerschlag, M. R., Cummings, C., Roblin, P. M., Williams, T. H., and Delke, I.: Efficacy of neonatal ocular prophylaxis for the prevention of chlamydial and gonococcal conjunctivitis. N. Engl. J. Med. 320:769, 1989.

7. Rice, R. J., Biddle, J. W., Jean Louis, Y. A., Dewitt, W. E., Blount, J. H., and Morse, S. A.: Chromosomally mediated resistance in *Neisseria gonorrhoeae* in the United States. Results of surveillance and reporting, 1983-84. J. Infect. Dis. 153:340, 1986.

8. Morse, S. A., Johnson, S. R., Biddle, J. W., and Roberts, M. C.: High-level tetracycline resistance in *Neisseria gonorrhoeae* is result of acquisition of streptococcal tetM determinant. Antimicrob. Agents Chemother. 30:664, 1986.

9. Knapp, J. S., Zenilman, J. M., Biddle, J. W., Perkins, G. H., Dewitt, W. E., and Thomas, M. L.: Frequency and distribution in the United States of strains of *Neisseria gonorrhoeae* with plasmid-mediated, high-level resistance to tetracycline. J. Infect. Dis. 155:819, 1987.

10. Schachter, J., Grossman, M., Holt, J., Sweet, R., Goodner, E., and Mills, J.: Prospective study of chlamydial infection in neonates. Lancet 2:377, 1979.

11. Rothenberg, R.: Ophthalmia neonatorum due to *Neisseria gonorrhoeae*. Prevention and treatment. Sex. Transm. Dis. 6(suppl):189, 1979.

12. Whitley, R. J., Nahmias, A. J., Soong, S., Galasso, G. G., Fleming, C. L., and Alford, C. A.: Vidarabine therapy of neonatal herpes simplex virus infection. Pediatrics 66:495, 1980.

13. Nahmias, A. J., Visintine, A. M., Caldwell, D. R., and Wilson, L. A.: Eye infections with herpes simplex viruses in neonates. Surv. Ophthalmol. 21:100, 1976.

14. Gershenfeld, L.: Povidone-iodine as a topical antiseptic. Am. J. Surg. 94:938, 1957.

15. Saggers, B. A., and Stewart, G. T.: Polyvinylpyrrolidone-iodine. An assessment of antibacterial activity. J. Hyg. 62:509, 1964.

16. Mac Rae, S. M., Brown, B., and Edelhauser, H. F.: The corneal toxicity of presurgical skin antiseptics. Am. J. Ophthalmol. 97:221, 1984.

17. Wille, H.: Assessment of possible toxic effects of polyvinylpyrrolidone-iodine upon the human eye in conjunction with cataract extraction. An endothelial specular microscope study. Acta Ophthalmol. 60:955, 1982.

18. Bird, B. R., and Forrester, F. T.: Laboratory Diagnosis of *Chlamydia trachomatis* Infections. Atlanta, Centers for Disease Control, 1980, pp. 30–40.

19. Thomas, B. J.: The inactivation of *Chlamydia trachomatis* by Betadine solution. In Reber, H.: The Proceedings of the World Congress on Antisepsis. New York, H. P. Publishing, 1976, pp. 16–18.
20. Apt, L., Isenberg, S., Yoshimori, R., and Paez, J. H.: Chemical preparation of the eye in ophthalmic surgery. III. Effect of povidone-iodine on the conjunctiva. Arch. Ophthalmol. 102:728, 1984.
21. Hale, L. M.: Uses of povidone-iodine in ophthalmic surgery with comments upon its antimicrobial activity. In Polk, H. C., and Ehrenkranz, N.:Therapeutic Advances and New Clinical Implications. Norwalk, Purdue Frederick, 1977.
22. Plotkin, S. A.: The effect of povidone-iodine on several viruses. In Polk, H. C., and Ehrenkranz, N.: Therapeutic Advances and New Clinical Implications. Norwalk, Purdue Frederick, 1977.
23. Harbison, M. A., and Hammer, S. M.: Inactivation of human immunodeficiency virus by Betadine products and chlorhexidine. J. Acquired Immune Defic. Syndrome 2:16, 1989.
24. Prince, H. N., Nonemaker, W. S., Norgard, R. C., and Prince, D. L.: Drug resistance studies with topical antiseptics. J. Pharm. Sci. 67:1629, 1978.
25. Houang, E. T., Gilmore, O. J. A., Reid, C., and Shaw, E. J.: Absence of bacterial resistance to povidone iodine. J. Clin. Pathol. 29:752, 1976.
26. Parrott, P. L., Terry, P. M., Whitworth, B., Frawley, L., McGowan, J. E., Jr., and Sikes, R. K.: *Pseudomonas aeruginosa* peritonitis attributed to a contaminated iodophor solution—Georgia. MMWR 31:197, 1982.
27. Berkelman, R. L., Lewin, S., Allen, J. R., Anderson, R. L., Budnick, L. D., Shapiro, S., Friedman, S. M., Nicholas, P., Holzman, R. S., and Haley, R. W.: Pseudobacteremia attributed to contamination of povidone-iodine with *Pseudomonas cepacia*. Ann. Intern. Med. 95:32, 1981.
28. Craven, D. E., Moody, B., Connolly, M. G., Kollisch, N. R., Stottmeier, K. D., and McCabe, W. R.: Pseudobacteremia caused by povidone-iodine solution contaminated with *Pseudomonas cepacia*. N. Engl. J. Med. 305:621, 1981.
29. Berkelman, R. L., Holland, B. W., and Anderson, R. L.: Increased bactericidal activity of dilute preparations of povidone-iodine solutions. J. Clin. Microbiol. 15:635, 1982.
30. Lund, R. J., Kibel, M. A., Knight, G. J., and Van der Elst, C.: Prophylaxis against gonococcal ophthalmia neonatorum. S. Afr. Med. J. 72:620, 1987.

Ophthalmic miniature

The well-constructed scientific paper is the utilitarian zenith of language: it communicates more precisely and more fully than any other literary form, with the possible exception of the haiku. A scientific paper can contain a year's work and a lifetime's experience in a few pages.

The Economist, Dec. 23, 1989, p. 111

Listeria monocytogenes Keratitis

Gerald W. Zaidman, M.D., Philip Coudron, Ph.D., and Judy Piros, M.D.

We treated a farmer who had *Listeria monocytogenes* bacterial keratitis. Therapy with topical antibiotics was unsuccessful; it was necessary to treat the patient with topical and systemic penicillin and gentamicin. To elucidate the pathogenesis of this infection, we developed a rabbit model. Using the patient's strain of *L. monocytogenes*, we determined that the severity of the rabbit infection was dose-related. If we used an inoculum of more than 10^7 organisms, many of the features of the human *Listeria* keratitis were mimicked. We also found that treatment with either penicillin or gentamicin did not control the infection as well as using both antibiotics simultaneously, a combination which resulted in relatively rapid resolution of infection and no corneal scarring. The human and animal data indicate that *L. monocytogenes* can be a virulent corneal pathogen. *Listeria* corneal infections must be treated aggressively with both penicillin and gentamicin to prevent permanent visual loss.

ALTHOUGH *Listeria monocytogenes*, a common soil-based organism, is a frequent cause of veterinary infections, it is a rare cause of human disease. Only a few cases of human ocular listeriosis have been reported. We treated a farmer with *L. monocytogenes* keratitis, corneal ulceration, and limbal abscesses. This patient's infection ran an unusual clinical course and was poorly responsive to antibiotic therapy. To understand better the pathophysiologic characteristics of ocular listeriosis, we developed an animal model of this disease. This model was used to observe the natural course of *L. monocytogenes* keratoconjunctivitis and to determine the best therapeutic antibiotic regimen.

Accepted for publication Dec. 7, 1989.

From the Department of Ophthalmology, Westchester County Medical Center, New York Medical College, Valhalla, New York (Dr. Zaidman), and the Departments of Ophthalmology and Microbiology, McGuire Veterans Administration Hospital, Medical College of Virginia, Richmond, Virginia (Drs. Zaidman, Coudron, and Piros). This study was supported in part by a grant from Research to Prevent Blindness, Inc.

Reprint requests to Gerald W. Zaidman, M.D., Department of Ophthalmology, Westchester County Medical Center, Valhalla, NY 10595.

Case Report

A 39-year-old farmer and sawmill worker developed a red right eye for which he was treated with polymyxin B sulfate–neomycin sulfate–hydrocortisone eyedrops. Over the next week, while treating some of his cows for an eye infection, his eye worsened. Because of the deteriorating condition of his eye, the patient was treated by his ophthalmologist, over a six-week period, with trifluridine, atropine, tobramycin, vidarabine, topical prednisone, and oral prednisone. Eventually, the patient was referred to the cornea service of the McGuire Veterans Administration Hospital.

Examination disclosed a normal left eye. The visual acuity in the right eye was hand motions. The patient had a 4-mm central corneal ulcer with peripheral corneal infiltrates (Fig. 1). The cornea was thinned to 75% normal thickness. A 0.5-mm hypopyon was present. The intraocular pressure was normal, and the fundus could not be visualized.

The cornea was scraped and cultured, and the patient was hospitalized. Gram, Giemsa, and acid-fast stains were all negative for bacteria, fungi, or mycobacteria. Treatment consisted of hourly topical fortified gentamicin (14 mg/ml) and topical polymyxin B–neomycin sulfate (5 mg/ml). In the hospital, the condition of the patient's eye continued to deteriorate. Over the next few days, his visual acuity in the right eye changed to light perception, the ulcer increased to 6 mm in size, the hypopyon increased, and the cornea thinned to less than 50% thickness.

Seventy-two hours after admission, cultures grew an unknown gram-positive organism,

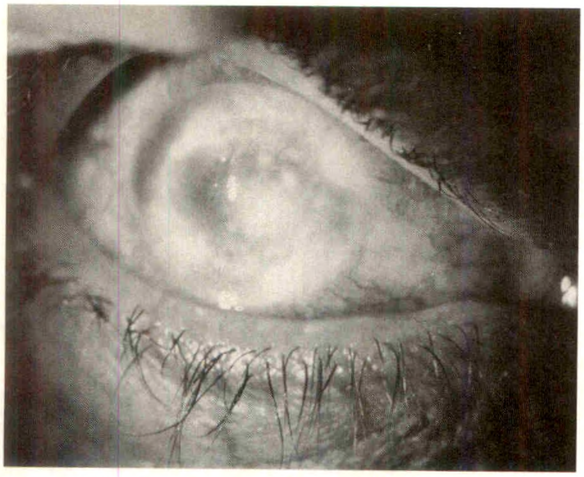


Fig. 1 (Zaidman, Coudron, and Piros). Slit-lamp photograph of eye of patient with a central corneal ulcer and peripheral corneal infiltrates.

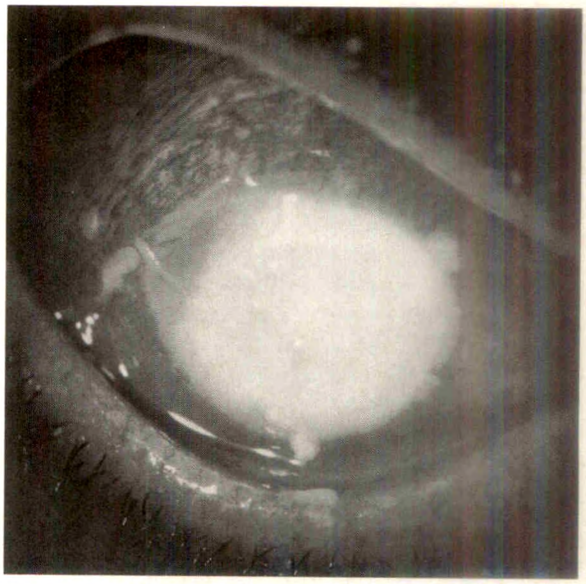


Fig. 2 (Zaidman, Coudron, and Piros). Slit-lamp photograph of infected eye, five days after admission to hospital. The ulcer has increased in size, and three limbal abscesses are now present.

which was sent to the state laboratory for analysis. At this time, the patient's treatment was changed to gentamicin (14 mg/ml) and penicillin G (100,000 U/ml) eyedrops every half hour. Natamycin 5% eyedrops were also administered, and periocular injections of ampicillin (50 mg) and gentamicin (20 mg) were given. The condition of the eye continued to worsen. The ulcer increased to 8 mm in size, and three limbal abscesses developed (Fig. 2). The cornea was rescraped and recultured, and a bandage contact lens was placed. Periocular clindamycin (20 mg) was administered, and the periocular gentamicin and ampicillin injections were repeated. Intravenous gentamicin, ampicillin, and clindamycin were started. Ten days after hospital admission, the state laboratory reported all cultures positive for *L. monocytogenes*. Therapy was changed to topical, periocular, and intravenous penicillin and gentamicin. Within 48 hours, the ulcer began to diminish. Over the next ten days, the abscesses and hypopyon disappeared, and the ulcer healed. Finally, a penetrating keratoplasty was performed. The patient now has a quiet eye with 20/20 visual acuity.

Material and Methods

We developed an animal model of *L. monocytogenes* keratitis, which was then used to investigate different antibiotic regimens in the therapy for the infection.

Eighteen female adult New Zealand white rabbits were used. All animals were maintained and handled in accordance with the Resolution on the Use of Animals in Research of the Association for Research in Vision and Ophthalmology. Care was exercised to prevent animal suffering and pain.

Before the study, all of the animals had normal anterior segments. Using the patient's strain of *L. monocytogenes*, two groups of New Zealand white rabbits were inoculated with either 2×10^5 or 2×10^7 organisms. Each group consisted of four rabbits (eight eyes). Another group of two rabbits (four eyes) were used as controls. The control eyes were inoculated with the sterile broth that had been used to cultivate the *L. monocytogenes* organism. Each rabbit was kept in a separate cage to minimize spread of the infection.

Daily penlight examinations were performed on each animal for 30 days. Slit-lamp examination or photodocumentation of clinically significant changes were performed as necessary. After one month, the rabbits were examined once weekly.

At the start of the experiment, the inoculum was dropped into each animal's conjunctival cul-de-sac. No topical anesthesia was used, and the eyes were closed manually for 20 seconds.

The conjunctiva of each rabbit eye was cul-

tured before inoculation and three, seven, ten, 14, 21, and 30 days after inoculation. Corneal scrapings for bacterial cultures were performed when necessary. All specimens were directly plated onto sheep's blood agar and chocolate agar. All culture plates were kept for a minimum of seven days before they were discarded.

To test antibiotic effectiveness, a fresh group of eight female New Zealand white rabbits was used. Conjunctival cultures were performed before the experiment. All animals had normal eyes. As a result of the first experiment, we inoculated each animal with 2×10^7 organisms of *L. monocytogenes* into the conjunctival cul-de-sac. The animals were then divided into three treatment groups. The first group of three rabbits (six eyes) received topical penicillin, 100,000 U/ml, one drop six times a day. The second group of three rabbits (six eyes) received topical gentamicin, 10 mg/ml, one drop six times a day. The third group of two rabbits (four eyes) received both topical penicillin (100,000 U/ml), and topical gentamicin (10 mg/ml), one drop of each six times a day. In each group, treatment began 36 hours after inoculation of the animals' eyes. Conjunctival cultures were performed 24 hours after inoculation (12 hours before therapy) and one, three, seven, 14, and 30 days after inoculation. Corneal scrapings were performed when necessary. All specimens were directly plated onto sheep's blood agar and chocolate agar, and all cultures were kept for at least seven days. Daily penlight examinations were performed on each animal for 30 days, and after that, once weekly.

Results

In the control eyes, only minimal conjunctival inflammation was present for two or three days (Table 1). No infection occurred, and all cultures were always negative. There were no sequelae, and the animals had normal eyes at three months.

Most of the eyes inoculated with *L. monocytogenes* developed clinical signs of *Listeria* keratoconjunctivitis. The infection was dose-related; one half of the animals inoculated with 2×10^5 organisms developed ocular listeriosis, but all eight eyes inoculated with 2×10^7 organisms became infected. Each eye that became infected, regardless of dose of inoculum, followed a similar course. Within 72 hours of inoculation,

TABLE 1
ANIMAL MODEL OF *LISTERIA* KERATITIS

DOSE OF INOCULUM	TIME AFTER INOCULATION				
	3 DAYS	7 DAYS	14 DAYS	4 WKS	6 WKS
None (4 control eyes)					
Positive cultures	0	0	0	0	0
Inflamed eyes	1	0	0	0	0
Corneal ulcers	0	0	0	0	0
2×10^5 Organisms (8 eyes)					
Positive cultures	3	3	0	0	0
Inflamed eyes	4	4	4	1	0
Corneal ulcers	0	3*	2	0	0†
2×10^7 Organisms (8 eyes)					
Positive cultures	8	7	0	0	0
Inflamed eyes	8	8	8	7	3
Corneal ulcers	0	7‡	8	0	0§

*Limbal abscesses in one eye.
†Corneal scarring in one eye.
‡Limbal abscesses in two eyes.
§Corneal scarring in eight eyes.

four of the eight eyes in the 10^5-organisms group and all eight eyes in the 10^7-organisms group had a thick, mucoid, purulent conjunctivitis with massive discharge. Many of the eyelids were stuck shut and could be pried open

Fig. 3 (Zaidman, Coudron, and Piros). *Listeria* corneal ulceration in untreated rabbit eye seven days after inoculation with 2×10^5 organisms.

only with effort. The cornea at this time was still normal. By day 7, corneal ulceration (Fig. 3) had occurred in three of eight eyes in the 10^5-organisms group and in seven of eight eyes in the 10^7-organisms group. One animal in the 10^5-organisms group had developed limbal abscesses, whereas two animals in the 10^7-organisms group had limbal abscesses. This was the peak of the infection in all eyes. Subsequently, the infection began to decrease slowly as the discharge, redness, and keratitis began to resolve. Spontaneous resolution of the *L. monocytogenes* keratoconjunctivitis was slow; at one month after inoculation, one eye in the 10^5-organisms group and seven eyes in the 10^7-organisms group were still inflamed.

The ocular cultures (Table 1) reflected the clinical disease. In the 10^5-organisms group, only three of four of the clinically infected eyes were culture-positive for *L. monocytogenes* at days 3 and 7. The uninfected eyes had negative cultures. In the 10^7-organisms group, initially all eight and then seven of the infected eyes were culture-positive at days 3 and 7. In both groups, any eye with a corneal ulcer or limbal abscesses had positive corneal cultures for *L. monocytogenes*. By day 14, as the clinical disease resolved, the cultures had spontaneously reverted to negative in all 16 inoculated eyes and in all 12 infected eyes.

Long-term sequelae were also dose-related. Three of the eight infected eyes in the 10^5-organisms group and all eight infected eyes in the 10^7-organisms group developed corneal scarring. The severity of the scarring was related to the severity of the infection. In one rabbit eye, phthisis developed, presumably secondary to unrecognized corneal microperforation.

Twenty-four hours after inoculation (12 hours before antibiotic therapy) with 2×10^7 organisms, all eight animals (16 eyes) showed evidence of severe conjunctival inflammation (Table 2). Fifteen of the 16 cultures done at this time were positive for *L. monocytogenes*. The animals were then segregated into the three treatment groups. One group received treatment with penicillin alone, another group received gentamicin alone, and the third group received penicillin and gentamicin. Twenty-four hours after the onset of antibiotic therapy, all 16 eyes still had severe conjunctival inflammation, and all 16 cultures were positive. No obvious corneal involvement was present at this time. Three days after treatment, all six eyes in the penicillin group and all six eyes in the gentamicin group still had conjunctivitis. Only one of the four eyes in the penicillin and gentamicin group, however, was inflamed; the other three eyes had resolved. Additionally all six cultures in the penicillin group and all six cultures in the gentamicin group were still positive for *L. monocytogenes*; however, all four cultures in the penicillin and gentamicin group had become negative. Seven days after therapy began, the 12 eyes in the penicillin or gentamicin groups still showed mild conjunctival inflammation; at this time, however, all 12 cultures were negative (and remained negative for the duration of the study). By this time, the four eyes in the penicillin and gentamicin group were totally normal without any evidence of inflammation, and all four cultures were negative. These four eyes remained quiet and uninflamed for the remainder of the experiment.

TABLE 2

EFFECTIVENESS OF ANTIBIOTICS AGAINST *LISTERIA* KERATITIS IN RABBITS (2×10^7 ORGANISMS)

ANTIBIOTIC REGIMEN	TIME AFTER ONSET OF THERAPY 1 DAY	3 DAYS	7 DAYS	14 DAYS	6 WKS
Penicillin (6 eyes)					
Positive cultures	6	6	0	0	0
Inflamed eyes	6	6	6	0	0
Corneal ulcers	0	0	0	0	0*
Gentamicin (6 eyes)					
Positive cultures	6	6	0	0	0
Inflamed eyes	6	6	6	1	0
Corneal ulcers	0	0	0	0	0†
Penicillin and gentamicin (4 eyes)					
Positive cultures	4	0	0	0	0
Inflamed eyes	4	1	0	0	0
Corneal ulcers	0	0	0	0	0

*Mild corneal scarring in one eye.
†Mild corneal scarring in two eyes.

Fourteen days after the onset of therapy, all six eyes in the penicillin group were quiet and uninflamed. One eye in the gentamicin group, however, still had evidence of mild conjunctivitis, and this persisted until the 17th day after the onset of treatment. Therefore, it took nearly three weeks for all six eyes in the gentamicin group to become quiet and uninflamed.

At no time during the study was obvious keratitis present. However, re-examination of the rabbit eyes six weeks and three months after

the study began showed that one eye in the penicillin group and two eyes in the gentamicin group had small corneal scars, whereas the penicillin and gentamicin group had normal anterior segments.

Discussion

Listeria monocytogenes has been recognized as an animal pathogen for many years. In animals, especially livestock and poultry, it causes conjunctivitis, spontaneous abortions, stillbirths, and sepsis.[1,2] Recently, *L. monocytogenes* has been recognized as a human pathogen in neonates, the elderly, and immunosuppressed patients. In these groups, it is an important cause of sepsis or meningitis.[3,4]

Human ocular listeriosis, however, remains rare. Cases of conjunctivitis and endophthalmitis have been reported.[5-8] Most of these incidences of disease have been in poultry handlers or farmers.[9] Recently, a case of an *L. monocytogenes* ring ulcer was reported in an elderly, diabetic woman.[10]

In some ways, the case described herein is similar to previously reported cases of human *Listeria* infection. The patient was a farmer who was handling infected animals. He had received previous therapy with topical corticosteroids, which presumably led to local ocular immunosuppression. Delay in diagnosis and continued use of corticosteroids permitted the keratitis to aggressively spread throughout the cornea. Eventually, limbal abscesses developed. Though limbal abscesses are an uncommon complication of bacterial keratitis, granulomatous lesions and abscesses are frequent findings in disseminated cases of human listeriosis.[4,7]

We also were surprised by this patient's poor response to antibiotic therapy. Our usual clinical regimen is to treat initially any unidentified gram-positive bacterial keratitis with broad-spectrum topical antibiotics (gentamicin and neomycin-polymyxin or cefazolin), which is usually successful. Unexpectedly, the patient's infection rapidly worsened with treatment. Only after treatment with topical and systemic penicillin and gentamicin was there any improvement.

The unusual clinical aspects of this infection motivated us to investigate the pathogenesis of ocular listeriosis. The animal experiments confirmed Koch's postulates for a pathogenic organism.[11] The organism that had infected this patient's eye was isolated in culture, inoculated onto an experimental animal, causing an infection similar to the human form, and then was recovered, isolated, and cultured. Additionally, we found that the *Listeria* organism has a fairly low level of virulence, but when it is present in sufficient quantity, it can produce a devastating infection. Our experiments demonstrated that in immunocompetent animals, 2×10^7 organisms were always successful in producing a severe infection; 2×10^6 organisms would cause keratoconjunctivitis in only one half of the animals. The untreated clinical infection produced in the rabbit eyes (2×10^7 organisms) was essentially identical to the clinical infection observed in our patient, that is, severe purulent keratoconjunctivitis complicated by slow progression to scleral involvement and limbal abscess formation. The animal experiments also showed that under the right conditions, immunosuppression is not necessary for the development of a severe *Listeria* infection. None of the animals were pretreated with topical or systemic corticosteroids; a high enough dose (more than 10^7 organisms) of inoculum was sufficient to consistently produce clinical infection. Finally, our antibiotic study confirmed our clinical impression that though penicillin and gentamicin alone were somewhat effective in eradicating the infection, a combination of penicillin and gentamicin was most effective. Animal eyes treated with this combination did not suffer any long-term complications.

Listeria monocytogenes is a slow-growing, gram-positive organism that can be confused with a diphtheroid.[4,7] Thus, some laboratories may ignore the organism's pathogenic potential and discard the culture plates. Our studies indicate that ophthalmologists should consider *L. monocytogenes* as a potentially important and serious pathogen. It should be considered in cases of indolent bacterial keratitis poorly responsive to traditional antibiotic therapy. It should also be suspected in patients who have frequent contact with animals (such as farmers, poultry handlers, and zookeepers), or in cases of bacterial keratitis that develop limbal abscesses. Topically or systemically immunosuppressed patients are also at high risk for *Listeria* keratitis. When the diagnosis of ocular listeriosis is suspected or confirmed, treatment should consist of a combination of penicillin and gentamicin.

References

1. Gray, M. L., Singh, C., and Thorp, F.: Abortion, stillbirth, early death of young rabbits by *Listeria monocytogenes*. I. Ocular instillation. Proc. Soc. Exp. Biol. Med. 89:163, 1955.
2. Kummerieje, K., and Mikkelsen, T.: Isolation of *Listeria monocytogenes* type 04 from cases of kerato-conjunctivitis in cattle and sheep. Nord. Vet. Med. 27:144, 1975.
3. Aubertin, E., de Rosnay, C. D., Aubertin, J., Veaux, R., Latrille, J., and Duriez, J. C.: Quelques aspects des listerioses de l'adulte. J. Med. Bordeaux 141:1243, 1964.
4. Koneman, E. W., Allen, S. D., Dowell, V. R., and Sommers, H. M.: Color Atlas and Textbook of Diagnostic Microbiology, ed. 2. New York, J. B. Lippincott, 1983, pp. 335–336.
5. Goodner, E. K., and Okumoto, M.: Intraocular listeriosis. Am. J. Ophthalmol. 64:682, 1967.
6. Bagnarello, A. G., Berlin, A. J., Weinstein, A. J., McHenry, M. C., and O'Connor, P. S.: *Listeria monocytogenes* endophthalmitis. Arch. Ophthalmol. 95:1004, 1977.
7. Snead, J. W., Stern, W. H., Whitcher, J. P., and Okumoto, M.: *Listeria monocytogenes* endophthalmitis. Am. J. Ophthalmol. 84:337, 1977.
8. Abbott, R. L., Forster, R. K., and Rebell, G.: *Listeria monocytogenes* endophthalmitis with a black hypopyon. Am. J. Ophthalmol. 86:715, 1978.
9. Felsenfeld, O.: Diseases of poultry transmissible to man. Iowa State Coll. Vet. 13:89, 1951.
10. Holbach, L. M., Bialasiewicz, A. A., and Boltze, H. J.: Necrotizing ring ulcer of the cornea caused by exogenous *Listeria monocytogenes* serotype IV b infection. Am. J. Ophthalmol. 106:105, 1988.
11. Joklik, W. K., Willett, H. P., Amos, B. B., and Wilfert, C. B.: Zinsser's Microbiology, ed. 19. Norwalk, Connecticut, Appleton & Lange, 1988, p. 3.

AMERICAN JOURNAL OF OPHTHALMOLOGY®

FRANK W. NEWELL, *Publisher and Editor-in-Chief*
Suite 1415, 435 North Michigan Ave., Chicago, Illinois 60611

Published monthly by the OPHTHALMIC PUBLISHING COMPANY
Suite 1415, 435 North Michigan Avenue, Chicago, Illinois 60611

PERSPECTIVES

Competition and Ophthalmology

Joseph C. Noreika, M.D.

Five primary issues shape current health-care policy: the allocation of increasingly scarce resources[1]; the necessary tradeoffs between cost of care and quality of care[2]; the escalating demand for health care because of an aging population, new therapeutic innovations and technology, the spread of the acquired immune deficiency syndrome, and the sequelae of drug addiction[3]; the societal inequities in the provision of health care to the poor, near-poor, and uninsured[4]; and the increasingly competitive marketplace in which physicians provide their services.[5] Growing competition may have the greatest impact on the day-to-day management of a medical practice and is arguably the domain over which individual practitioners exert the greatest control.

Competition is not new to health care. In the United States, 19th century healers of various talent and skill shamelessly promoted their prescriptions to an unsophisticated clientele. Even after medicine became better organized in the latter part of the 19th century, competing factions of physicians fought turf wars in the urban centers.[6] What is novel about today's competitive environment is that the government approves of its propagation. Although universal health care with its implicit socialism and care rationing has received much attention, an alternate model for the future American health-care system incorporates competition among providers as its keystone.[7]

The concept that competition between practitioners will better allocate resources reaches back to the fundamentals of Adam Smith's text, The Wealth of Nations. The opponents of or-

ganized medicine argue that its cartel arrangement and the high barriers of entry to a medical career prevent natural market forces from lowering prices and better distributing resources. They contend that it is an imperfection of the American capitalistic system, which has permitted physicians the opportunity to exploit their position for economic gain. These opponents state that, as a result, ours is the most expensive health-care system with the highest paid and most collusive practitioners in the world.[8] The implications for the United States of a less expensive health-care system with less well-compensated attendants are unknown. Experience from other countries' efforts at centrally controlled health-care policy indicates that significant tradeoffs must be accepted.[9]

The framework by which I will explore competition in ophthalmology relies heavily on the concepts of Michael Porter of the Harvard Business School. His work, Competitive Strategy, is recognized in industry as an important contribution to our understanding of competition, its ramifications, and its effects on strategic policy.[10] Although much of what follows may be intuitively grasped by physicians experienced in running their businesses, it offers an organized structure to examine assumptions that may not be appropriate in today's environment. For the physician-in-training or the less experienced physician, it offers an opportunity to consider aspects of practice often overlooked when planning a career or a vocational change.

The model emphasizes five primary competitive forces that define and shape an industry's structure. The industry in which a business or practice operates is a more important determinant of ultimate success than the relative excellence or incompetence of the individual firm. It might be argued that ophthalmologists with little business acumen were highly successful in the past not only because of their own contributions but because the demand for care exceeded the supply of care givers and there was little governmental intervention, little need for risk analysis in the procurement of capital equipment, and excellent cash flow because of high remuneration for services with relatively low overhead expense. It is different today. Clinical excellence is no longer sufficient to guarantee success and financial security.

The five competitive forces are as follows: existing rivals; new entrants; substitutes; buyers; and suppliers. Essential to this framework of competition is government regulation.

Existing Rivals—Typically, the practitioners down the street are considered the prototypical ophthalmic competitors. They may be the most easily identified and most visible. They are not, however, the most important.

Ophthalmologists have never held a monopoly on eye care. Macroeconomically, they are an oligopoly, that is, a group of relatively few competitors who are more or less equal with little differentiation in the eyes of the patient and who must be, to some extent, mutually dependent (for example, coverage of hospital emergency rooms and practices; continuing education; involvement in the political arena). As reimbursement levels have fallen, practices have found it necessary to expand. Thus, practitioners, locations, and services have been added, which has resulted in increased capacity in the profession. In health care, excess capacity does not leave the industry readily. Older physicians tend to remain in marginal practices and administer to patients who might otherwise seek care elsewhere.

Patients do benefit, however. They are better served because they are not forced to wait months for care. But the physician is faced with the challenge of filling that expanded capacity, which carries a price of high, fixed building costs, technology, and personnel. Thus, more physicians are providing evening and weekend hours, promoting their practices through expensive media and direct mail advertisement, and actively courting the favor of referral sources if not buying their goodwill outright.

As competition has increased among rivals, it has fueled a positive feedback cycle of increasing costs, decreasing margins, and competitive retaliation. Competition does not occur in a vacuum. Whenever ophthalmologists plan a change in the strategic direction of their practices, it is advisable to consider the possible reactions of their primary rivals. The costs involved with increased competition are particularly troublesome because, once initiated, they are difficult to control and impossible to cut back without adversely affecting business.

New Entrants—It is estimated that there are 1,955 physicians currently in ophthalmic training programs in the United States.[11] These physicians represent more than 13% of all ophthalmologists involved in patient care. New training positions are being added each year despite that these physicians must be accommodated in a system that will have a significant surplus of practitioners by the year 2000.[12] Because these new specialists will face high barriers to entry because of the cost of capital

equipment and skilled staff, fewer locales without significant competition, and the burden of educational debt, most will seek positions of employment in established groups and managed health-care organizations. Recent data suggest that the price commanded by physicians just out of training has already begun to fall.[13]

Less apparent sources of new entry may be more significant because they control prodigious resources and have greater practice-management experience. Acquisitions of existing practices by traditional referral-based groups and teaching centers are an attempt to decentralize and capture a larger patient pool. In an effort to increase their caseload, aggressive cataract surgeons seek older, decaying practices in an attempt to acquire the expected backlog of patients who require care. Even entrepreneurial venture capitalists are willing to bankroll surgeons establishing a practice in exchange for a guaranteed share of the profits.

Because all ophthalmologists compete for a finite share of patients, a fraction of whom have diseases, competition must increase. After a decade of continual growth following the diffusion of intraocular lens technology, the cataract surgery industry appears to be leveling off despite the graying of America. Because of low industry growth, competition has intensified. Practices vie to differentiate themselves from their competitors and erect entry barriers. Services are duplicated. Economic resources are wasted. Profitability suffers. The cost of health care appears to accelerate less rapidly in areas of intense competition. This is a fundamental argument of those advocating the competitive model for American health care.

Substitutes—The most visible substitute for the ophthalmologist is the optometrist. It can be maintained that the optometric profession is faced with greater threats than is ophthalmology. Perhaps because of its greater perception of danger, it has been active in seeking legislative relief in expanding its professional domain. Half of the states now have optometric therapeutic drug laws.

Because most optometrists realize that they cannot compete against ophthalmologists in rendering medical eye care, they have successfully attracted patients by offering convenience, accessibility, and service. A well-conceived public relations campaign designed to strengthen the identification of optometry as the primary eye-care provider has met with some success among the public, managed health-care organizations, and legislators. Ophthalmologists would be wise to remember that the benefits of a given service are defined by those receiving the service and not by those providing it.[14] If the public perceives that there is adequate value at an acceptable price (a good price/performance ratio) for an optometrist's service, optometrists will remain a viable competitive force to the ophthalmologist.

There may be other less well-recognized substitutes for an ophthalmologist's care. In areas where supposed laser cataract surgery has been popularized, surgeons performing planned extracapsular cataract extraction might find themselves at a competitive disadvantage to those promoting phacoemulsification. Patient awareness of the competing technologies is the key issue. Approximately 650 to 750 new phacoemulsification units are sold each year.

Future substitutes for the ophthalmologist might include the increased use of robotics in surgical procedures and pharmacologic prophylaxis of disorders that previously required surgical intervention. The diffusion of such technology lowers the demand for the costly labor-intensive skills of the ophthalmologist. The anticipated commercialization of the excimer laser relative to refractive surgery is a powerful example of how an entire segment of an industry, opticianry, could face the same challenges as past builders of steam locomotives and vacuum tubes.[15]

As patients become more sophisticated, they will demand higher levels of service. Patients will define the level of service by patronizing those practices that offer accessibility, affordability, and personal and empathic care.

Buyers—With the explosion of managed care and third-party reimbursement, the patient is no longer the buyer of health-care services. Indeed, with the diffusion of health maintenance organizations, independent practice associations, and preferred provider organizations, it is unlikely that the patient will be free to choose the provider. The power of the buyer of health care is the crucial element of competition because it is the buyer who can concentrate economic power to the financial detriment of the individual practitioner.

Before the mid-1940s, individual patients were the buyers of health care. When industry began to offer health-care benefits to its employees, the actual buyers of services began to consolidate. With consolidation came the power to dictate more services and better quality of care, and then lower costs. Perhaps because

American industry functioned relatively unopposed in the international marketplace until the early 1970s, there was little impetus to become involved in monitoring the cost of this fringe benefit. Now international competition is forcing many businesses to cut expenses to maintain their competitiveness, and health-care costs are now being scrutinized by corporations seeking to avoid financial disadvantage.[16] Battlelines between unionized employees and corporate management form over the issue of health-care benefits.[17] Americans want more and better health care but are reluctant to pay for it.

The actual buyers of health care will continue to seek less expensive means to provide benefits to their dependents. Whereas individual patients exhibit loyalty to their physicians, large corporations show little aversion to switching providers in order to enhance their bottomline for shareholders. Favored status will be awarded on the basis of which practices can provide quality care efficiently and at a lower cost to the buyer.

Ophthalmology is under pressure because the federal government through its Medicare endowment is a principal buyer of eye-care services. In an era of budget deficits and scarce resources, the urgency to reduce prices will continue. Because congress has the power to impose unilateral restrictions and sanctions on ophthalmic services, this imbalance of power and the relative impotence of the subspecialty remain the most important threat to the status quo.

Managed health-care organizations are also competing for patients. After the shakeout of the late 1980s, the survivors are again profitable and the outlook on Wall Street appears bright. It might be argued that closed-panel health maintenance organizations are better defined as substitute providers because their ophthalmologist-employees are competing for a defined patient pool with nonaffiliated physicians. On the other hand, open-panel managed health-care organizations must be classified as buyers and will attempt to drive down the price of care rendered by their panel of physicians to increase profitability. Because the federal government currently favors the expansion of managed care in this country, attempts by loosely organized practitioners to exclude these organizations have met with the threat of antitrust litigation.

As the buyers of health care become more consolidated, their power will increase. There will be increasing pressure to lower prices, which will intensify the competition among ophthalmologists who seek to maintain their revenues. It is a foregone conclusion that profitability will suffer.

Suppliers—There are three primary suppliers to the ophthalmologist: equipment and technology vendors; hospitals; and labor. All suppliers can demand increased input prices and all can adversely influence practice costs.

The vendors of ophthalmic supplies, including capital equipment, contact and intraocular lenses, and pharmaceuticals, have become more integrated as American industry has evolved. Although many products, such as intraocular lenses, have been reduced to the status of commodities and are marketed on the basis of price, this may not persist as fewer companies remain viable competitors. Companies can maintain artificially high prices on new technology that is perceived by ophthalmologists to provide a competitive advantage. These profit centers can be sustained until the technology becomes sufficiently dispersed to force prices down. Continual innovation on the base technology, however, will guarantee the need to update lest one run the risk of being out-of-date.

Hospitals can be an important competitive force for ophthalmologists because of the hospitals' concentration relative to the larger pool of physicians and their importance as a workshop and source of patients. Because the status of many procedures and their reimbursement has changed drastically, ophthalmologists are less consequential to hospitals than in the recent past. Hospital profitability is generally linked to occupancy, and ophthalmologists simply do not fill many beds with patients.

Hospitals can compete with individual practitioners on many levels. They can encourage new entrants to the specialty, decrease the services available to the physician, increase the indirect and opportunity costs implicit in maintaining hospital privileges, and demand risk-sharing when considering the acquisition of new technology.[18] The hospital remains the primary workshop of ophthalmic surgeons, but many ophthalmologists have been forced to accept the financial risks of managing their own surgical facility because of an antagonistic environment.

Another element of an ophthalmic practice that generates significant leverage is labor. Because medicine is labor-intensive, personnel costs have and will continue to constitute a significant portion of practice expense. Labor is

becoming scarcer as industries compete for a dwindling pool of eligible workers. Whereas there may be an oversupply of ophthalmologists, ophthalmic clerical and technical support staff will increasingly be in demand.

Ophthalmic technicians may be especially important because demands for practice efficiency or, more correctly, process efficiency will necessitate the use of ophthalmic technicians as "physician-extenders," that is, staff employed to allow the more costly physician to work as productively as possible. The price paid for these employees will continue to rise in the future, especially if the nation's economy remains robust. Because much of the ophthalmic support work force consists of women, concessions to life-style will become more significant when recruiting and hiring. Creative human-resource management will become more important and will entail direct, indirect, and opportunity costs to the physician.

Today, ophthalmologists find themselves in a profession that bears little resemblance to what they had come to expect. Like Siu's Chinese baseball where the game is the same as traditional baseball except that, when the ball leaves the pitcher's hand and is in the air, anyone can move any of the bases anywhere, ophthalmologists are trying to treat their patients and run their businesses while the rules are constantly changing.[19] In this environment, the cognitive skills prized by physicians in the diagnosis and treatment of disease offer little comfort and consolation in the management of their practices.

Each of the five potential influences of competition in ophthalmology wields variable power and distinctive influence. Because of the essence of health care to society, government has come to play an increasingly important role in determining the relationships between the five forces. It has been postulated that decay of advanced industrial societies occurs when too many special interest groups influence government policy to insure their position. Perhaps that is the unenviable position in which ophthalmology now finds itself. Seen as a small special interest group by legislators, its power to effect change to its benefit is minimal compared to other well-established special interests, such as labor unions, corporations, senior citizens, and the underserved.[20] It behooves ophthalmologists to understand better those forces that will affect their future livelihood.

Whereas enormous resources are spent attempting to differentiate practices from other nearby practices to gain patient share and shortlived advantage, ophthalmologists might be wiser to reaffirm their sense of profession and present a unified front to their other, stronger competitors, especially those buying their services. Otherwise, the independent ophthalmology practice will run the risk of duplicating the historic disappearance of the corner grocer. Not that ophthalmologists should not strive to provide excellent and timely service to their patients: to the contrary, if ophthalmologists hope to capture power and have a voice in policy, they will need the support of patients, who are the country's consumers and electorate. Dollars disbursed to identity and fulfill the true needs of patients will be more efficiently spent than resources squandered on duplicate technologies, media advertisement, and inefficient practice.

Despite the changes of the last decade, medicine remains a growth industry. To capture an equitable and just share of the value created by ophthalmologists in the industry, ophthalmologists must reassert the power implicit in their status as professionals. The essence of this power is found in the public recognition of the physician's duty to put the patient's good ahead of individual gain and avarice. The Federal Trade Commission has legally defined the practice of medicine as a trade. Acquiescing to the temptations of commercialism, ophthalmologists can increasingly vie among themselves, dissipating capital and permanently crippling their professional status. Once that privileged state is lost, the entitlement of autonomy and self-regulation, already threatened, will be ceded.

If the ophthalmology profession is to remain a viable force into the next century, unity and cooperation among practitioners will be essential to negotiate from a position of strength with potent, better-connected, self-interest groups.

Reprint requests to Joseph C. Noreika, M.D., Reserve Park I, Ste. 70, 3637 Medina Rd., Medina, OH 44256.

References

1. Welch, H. G., and Larson, E. B.: Dealing with limited resources. The Oregon decision to curtail

funding for organ transplantation. N. Engl. J. Med. 319:171, 1988.

2. Leaf, A.: Cost effectiveness as a criterion for Medicare coverage. N. Engl. J. Med. 321:898, 1989.

3. Berk, M. L., Monheit, A. C., and Hagan, M. M.: How the U.S. spent its health care dollar. 1929-1980. Health Aff. 7:46, 1988.

4. Thorpe, K. E., and Siegel, J. E.: Covering the uninsured. Interactions among public and private sector strategies. JAMA 262:2114, 1989.

5. Paris, E.: Hippocrates meets Adam Smith. Forbes 137(3):63, 1986.

6. Starr, P.: The Social Transformation of American Medicine. New York, Basic Books, 1982, pp. 79–144.

7. Enthoven, A., and Kronick, R.: A consumer-choice health plan for the 1990s. Universal health insurance in a system designed to promote quality and economy (parts I and II). N. Engl. J. Med. 320:29,94, 1989.

8. Schieber, G. J.: Health care expenditures and utilization abroad. Implications for the U.S. J. Med. Pract. Management 4:16, 1988.

9. Evans, R. G., Lomas, J., Barer, M. L., Labelle, R. J., Fooks, C., Stoddart, G. L., Anderson, G. M., Feeny, D., Gafni, A., Torrance, G. W., and Tholl, W. G.: Controlling health expenditures. The Canadian reality. N. Engl. J. Med. 320:571, 1989.

10. Porter, M. E.: Competitive Strategy. Techniques for Analyzing Industries and Competitors. New York, The Free Press, 1980, pp. 3–33 and 191–214.

11. Eiler, M. A., and Pasko, T. J.: Specialty Profiles. Chicago, American Medical Association, 1988, pp. 331–356.

12. Mulhausen, R., and McGee, J.: Physician need. An alternative projection from a study of large, prepaid group practices. JAMA 261:1930, 1989.

13. Torry, K.: New MDs' starting salaries down. Am. Med. News, Oct. 6, 1989.

14. Day, G. S., Shocker, A. D., and Srivastava, R. K.: Customer-oriented approaches to identifying product-markets. J. Marketing 43:8, 1979.

15. Rosegger, G.: The Economics of Production and Innovation. An Industrial Perspective, ed. 2. Oxford, Pergamon Press, 1986, pp. 199–229.

16. Gray, J.: How serious are employers about cutting health costs? Very. Med. Econ. 66(20):112, 1989.

17. Karr, A. R., and Carnevale, M. L.: Facing off over health-care benefits. Wall St. J., Aug. 11, 1989.

18. Goldsmith, J.: A radical prescription for hospitals. Harvard Bus. Rev. 67(3):104, 1989.

19. Siu, R. G. H.: Management and the art of Chinese baseball. Sloan Management Rev. 19:83, 1978.

20. Birnbaum, J. H.: Powerful medical lobby may be the big loser as congress attempts to rein in Medicare costs. Wall St. J., May 11, 1989.

LETTERS TO THE JOURNAL

Severe Ocular Anterior Segment Ischemia After Long-Term Trifluridine Treatment for Presumed Herpetic Keratitis

Douglas R. Shearer, M.D., and William M. Bourne, M.D.

Department of Ophthalmology, Mayo Clinic and Mayo Foundation.

Inquiries to William M. Bourne, M.D., Mayo Foundation, 200 First St. S.W., Rochester, MN 55905.

Falcon and associates[1] reported a case of conjunctival ischemia after chronic topical trifluridine treatment. We treated a patient with severe anterior segment ischemia that occurred after four months of topical trifluridine treatment for presumed herpetic keratitis.

A 61-year-old woman developed injection and irritation in her left eye. The patient previously had recurrent keratitis that was symptomatically similar to the current episode. Her ophthalmologist diagnosed herpes simplex keratitis and initiated treatment with trifluridine and prednisolone acetate. Trifluridine six to seven times daily and prednisolone four times daily were continued for over four months until the patient developed left supraorbital boring pain that prompted her referral to our institution. She had no history of significant medical problems or cardiovascular disease and was not taking any other medications. She had no previous ocular surgery or trauma.

Visual acuity was R.E.: 20/20 and L.E.: 20/400. The left pupil was mid-dilated and nonreactive, but no afferent pupillary defect was apparent. Visual fields by confrontation were full in each eye. There were pallor and chemosis of the left anterior bulbar and inferior palpebral conjunctiva with nonperfused conjunctival arteries and periphlebitic subconjunctival hemorrhages (Fig. 1). The entire left corneal and inferonasal conjunctival epithelium was disrupted as evidenced by fluorescein staining. There was diffuse corneal haze. The corneal thickness measured 0.61 mm by ultrasonic pachymetry. The left anterior chamber had a moderate cellular reaction with diffuse fine keratic precipitates and a small hypopyon. Intraocular pressure by Mackay-Marg tonometry was R.E.: 14 mm Hg and L.E.: 52 mm Hg. Examination of the posterior segment was normal in each eye. Fluorescein angiography of the anterior segment (Fig. 2) showed an absence of inferior palpebral and anterior bulbar conjunctival and episcleral perfusion with large areas of iris nonperfusion. Laboratory evaluation including a complete blood cell count with differential, serum glucose level, sedimentation rate, antinuclear antibody level, and rheumatoid factor was within normal limits. Both herpes simplex and varicella zoster titers were positive at 1:40 for IgG. IgM levels were not measurable. The trifluridine and prednisolone were discontinued, and acetazolamide and timolol were given with lowering of the intraocular pressure to 35 mm Hg. Over the ensuing five months, conjunctival neovascularization, cataract, band keratopathy, and iris atrophy have developed.

Anterior segment ischemia has resulted from temporal arteritis, hyperviscosity syndromes, disseminated intravascular coagulopathy, vascular disease, and ophthalmic surgical procedures.[2] None of these associated factors were apparent in this case. The ischemia may have been secondary to zoster ophthalmicus without

THE JOURNAL welcomes letters that describe unusual clinical or pathologic findings, experimental results, and new instruments or techniques. The title and the names of all authors appear in the Table of Contents and are retrievable through the Index Medicus and other standard indexing services. Letters must not duplicate data previously published or submitted for publication. Each letter must be accompanied by a signed disclosure statement and copyright transfer agreement published in each issue of THE JOURNAL.

Letters must be typewritten, double-spaced, on 8 1/2 x 11-inch bond paper with 1 1/2-inch margins on all four sides. (See Instructions to Authors.) An original and two copies of the typescript and figures must be sent. The letters should not exceed 500 words of text. A maximum of two black-and-white figures may be used; they should be cropped to a width of 3 inches (one column). Color figures cannot be used. References should be limited to five.

Letters may be referred to outside editorial referees for evaluation or may be reviewed by members of the Editorial Board. All letters are published promptly after acceptance. Authors do not receive galley proofs but if the editorial changes are extensive, the corrected typescript is submitted to them for approval.

These instructions markedly limit the opportunity for an extended discussion or review. Therefore, THE JOURNAL does not publish correspondence concerning previously published letters.

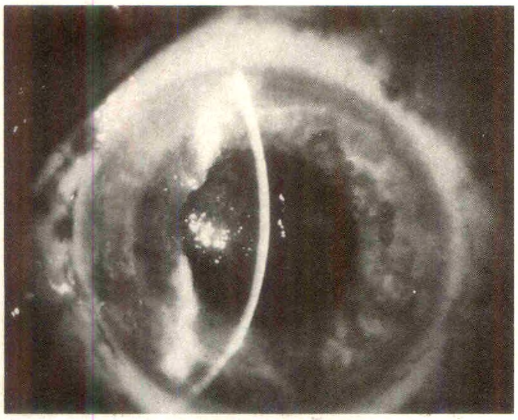


Fig. 1 (Shearer and Bourne). Bulbar subconjunctival hemorrhages, conjunctival pallor, disrupted corneal epithelium, and hypopyon.

an accompanying dermatologic manifestation, but the history of numerous similar recurrent episodes beginning at an early age makes this cause unlikely.[3] Although not previously reported, a virulent herpes simplex strain may have been responsible. The previous episodes were relatively mild, however, and the ischemic event occurred four months after this episode's initial onset. The toxic effects of trifluridine are similar to those of other topical antiviral agents, and include punctate epithelial keratopathy, follicular conjunctival hypertrophy, punctal occlusion, contact hypersensitivity, conjunctival cicatrization, and inhibition of corneal epithelial wound healing.[4] Additionally, a case of conjunctival ischemia from topical trifluridine has been reported.[1] Although an

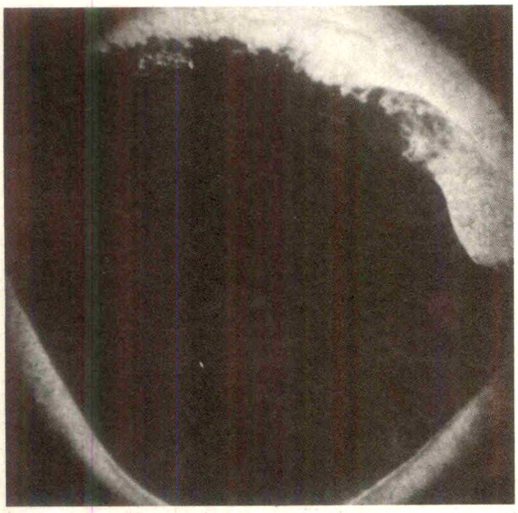


Fig. 2 (Shearer and Bourne). Anterior segment fluorescein angiogram demonstrating nonperfusion of the palpebral and bulbar conjunctiva and iris.

infectious vasculitis cannot be ruled out, we believe that a toxic effect of long-term topical trifluridine therapy is the most likely cause in this case.

References

1. Falcon, M. G., Jones, B. R., Williams, H. P., Wilhelmus, K., and Coster, D. J.: Adverse reactions in the eye from topical therapy with idoxuridine, adenine arabinoside and trifluorothymidine. In Sundmacher, R. (ed.): Herpetische Augenerkrankungen. München, J. F. Bergmann Verlag, 1981, pp. 263–268.
2. Crock, G.: Clinical syndromes of anterior segment ischemia. Trans. Ophthalmol. Soc. U.K. 87:513, 1967.
3. Naumann, G., Gass, J. D. M., and Font, R. L.: Histopathology of herpes zoster ophthalmicus. Am. J. Ophthalmol. 65:533, 1968.
4. Stern, G. A., and Killingsworth, D. W.: Complications of topical antimicrobial agents. Int. Ophthalmol. Clin. 29:137, 1989.

Combined Superior Oblique Paresis and Brown's Syndrome After Blepharoplasty

Kimberly A. Neely, M.D., J. Terry Ernest, M.D., and Marianne Mottier, C.O.

Department of Ophthalmology and Visual Science, University of Chicago. This study was supported in part by an unrestricted grant to the Department of Ophthalmology and Visual Science from Research to Prevent Blindness, Inc.

Inquiries to J. Terry Ernest, M.D., 939 E. 57th St., Chicago, IL 60637.

Complications of blepharoplasty include blepharoptosis, ectropion, and blindness.[1] Diplopia occurs less often and usually after injury to the inferior rectus or inferior oblique muscle.[2] We treated a patient who developed superior oblique muscle paresis later combined with Brown's syndrome after blepharoplasty.

A 59-year-old woman underwent bilateral upper eyelid blepharoplasty with fat removal under general anesthesia. An injection of lidocaine hydrochloride with epinephrine hydrochloride was given in the superonasal orbit bilaterally for hemostasis. Immediately after the operation, the patient noted double vision

ORTHO	ORTHO	ORTHO
LHT 8$^{\Delta}$	LHT 6$^{\Delta}$	ORTHO
LHT 14$^{\Delta}$ ET 4$^{\Delta}$	LHT 8$^{\Delta}$ ET 4$^{\Delta}$	LHT 8$^{\Delta}$ ET 4$^{\Delta}$

Head tilted to left:	LHT 10$^{\Delta}$ ET 4$^{\Delta}$
Head tilted to right:	trace left hyperphoria
Double Maddox rod:	5 degrees excyclodeviation, left eye

Fig. 1 (Neely, Ernest, and Mottier). Prism cover test in the nine cardinal positions of gaze and double Maddox test. Ocular motility measurements one week after blepharoplasty were consistent with left superior oblique muscle paresis.

RHT 12$^{\Delta}$	RHT 7$^{\Delta}$	ORTHO
RHT 7$^{\Delta}$	ORTHO	ORTHO
LHT 12$^{\Delta}$ ET 5$^{\Delta}$	LHT 6$^{\Delta}$ ET 5$^{\Delta}$	LHT 10$^{\Delta}$ ET 8$^{\Delta}$

Head tilted to left:	LH(T) 6$^{\Delta}$
Head tilted to right:	Orthophoria
Double Maddox rod:	No cyclodeviation

Fig. 2 (Neely, Ernest, and Mottier). Prism cover test in the nine cardinal positions of gaze and double Maddox test. Ocular motility measurements four weeks after surgery demonstrated restricted movement of the left eye in right upward gaze in addition to left superior oblique muscle paresis.

most severe when looking down and to the right. These symptoms persisted, and she was referred to our institution one week after the operation.

Examination showed that the patient had a right head tilt with chin depression. Ocular motility measurements showed a left hypertropia in primary gaze that increased on downward gaze, especially to the right (Fig. 1). Left head tilt increased the left hypertropia, while right head tilt produced only minimal left hyperphoria. Double Maddox rod testing in primary gaze demonstrated 5 degrees of excyclodeviation in the left eye. Versions were full except for decreased ability of the left eye to move downward and inward. We interpreted these findings as left superior oblique muscle weakness.

Three weeks after the operation, examination showed restricted movement of the left eye upward and inward. After four weeks, the patient was orthophoric in primary gaze. The cyclodeviation had resolved. Left eye hypodeviation on right-upward gaze was more pronounced, and left eye hyperdeviation in all directions of downgaze remained (Fig. 2). Forced ductions disclosed resistance to moving the left eye upward and inward consistent with Brown's syndrome.[3] Eight months after the operation, the patient had 4 prism diopters of left hypertropia in primary gaze, minimal left-eye hypodeviation in right-upward gaze, and 12 to 18 prism diopters of left-eye hyperdeviation in all fields of downward gaze.

There are few reports of superior oblique muscle injury after blepharoplasty. In 1975, Levine and associates reported postoperative diplopia caused by incarceration of the superior oblique tendon in the orbital septum.[4] Diplopia resolved after release of the tendon. In 1980, Wesley, Pollard, and McCord reported superior oblique muscle paresis after blepharoplasty.[5] Their patient complained of pain during cautery of fat in the superonasal upper eyelid and experienced diplopia postoperatively. Harley and associates later described a patient with superior oblique muscle paresis and another with Brown's syndrome after blepharoplasty.[2]

Our patient's problems may be explained by injury to the superior oblique muscle, tendon, or trochlea during resection and cautery of orbital fat or, perhaps, during local anesthetic injection. Resolution of the Brown's syndrome suggests resolution of edema or hematoma involving the superior oblique tendon or trochlea. Gradual worsening of the restriction in downward gaze suggests increasing fibrosis in the region of the superior oblique and superior rectus muscles.

References

1. Wiggs, E. O.: Blepharoplasty complications. Trans. Am. Acad. Ophthalmol. Otolaryngol. 81:OP-603, 1976.

2. Harley, R. D., Nelson, L. B., Flanagan, J. C., and Calhoun, J. H.: Ocular motility disturbances following cosmetic blepharoplasty. Arch. Ophthalmol. 104:542, 1986.

3. Brown, H. W.: Congenital structural muscle anomalies. In Allen, J. H. (ed.): Strabismus Ophthalmic Symposium, vol. 1. St. Louis, C. V. Mosby Company, 1950, pp. 205–236.

4. Levine, M. R., Boynton, J., Tenzel, R. R., and Miller, G. R.: Complications of blepharoplasty. Ophthalmic Surg. 6:53, 1975.

5. Wesley, R. E., Pollard, Z. F., and McCord, C. D.:

Superior oblique paresis after blepharoplasty. Plast. Reconstr. Surg. 66:283, 1980.

Acquired Brown's Syndrome After Peribulbar Anesthesia

J. C. Erie, M.D.

Department of Ophthalmology, Mayo Clinic and Mayo Foundation.

Inquiries to J. C. Erie, M.D., Mayo Clinic, 200 First St. S.W., Rochester, MN 55905.

Brown's syndrome, first described in 1950 by Brown,[1] is the inability to elevate the eye in the adducted position, both by voluntary and passive forced ductions. Since the original description, cases of acquired Brown's syndrome have been reported to occur after tucking of the superior oblique tendon, after surgery or trauma in the vicinity of the trochlea, and with inflammatory conditions of the superior oblique tendon.[2] I treated a patient with acquired Brown's syndrome after peribulbar anesthesia.

A 51-year-old woman had a left peribulbar injection in preparation for cataract extraction. The anesthesiologist injected 5 ml of a 60:40 mixture of lidocaine 4% and bupivacaine hydrochloride 0.75% mixed with 1 ml of hyaluronidase into the inferotemporal orbit, and 3 ml of the same mixture into the superonasal orbit using a 37-mm sharp, 25-gauge needle. The needle depth was approximately 2.5 cm and both injections were outside the muscle cone. The injection was uncomplicated, and no hemorrhage was noted. The injection was followed by application of a Honan balloon for 30 minutes at a pressure of 20 mm Hg. On the first postoperative day the patient had vertical diplopia. Preoperatively, she had no diplopia and rotations were normal.

I first examined the patient six months after the operation. The patient stated that her diplopia had remained unchanged. There was no palpable mass or tenderness in the superonasal quadrant of the left orbit. In primary gaze 10 prism diopters of left hypotropia was apparent; this increased to 30 prism diopters on right horizontal gaze and 35 prism diopters on right upward gaze. Rotations showed an inability to elevate the adducted left eye (Figure). Elevation on abduction was normal. Downshoot of the left eye was evident in attempted horizontal right gaze. Mild overaction of the left superior oblique was apparent. Forced ductions were positive on attempted elevation of the adducted left eye. Additionally, tension by applanation tonometry of the left eye increased from 12 mm Hg in primary gaze to 30 mm Hg when the patient attempted to elevate her adducted left eye. Results of a medical examination were normal. There was no evidence of rheumatoid

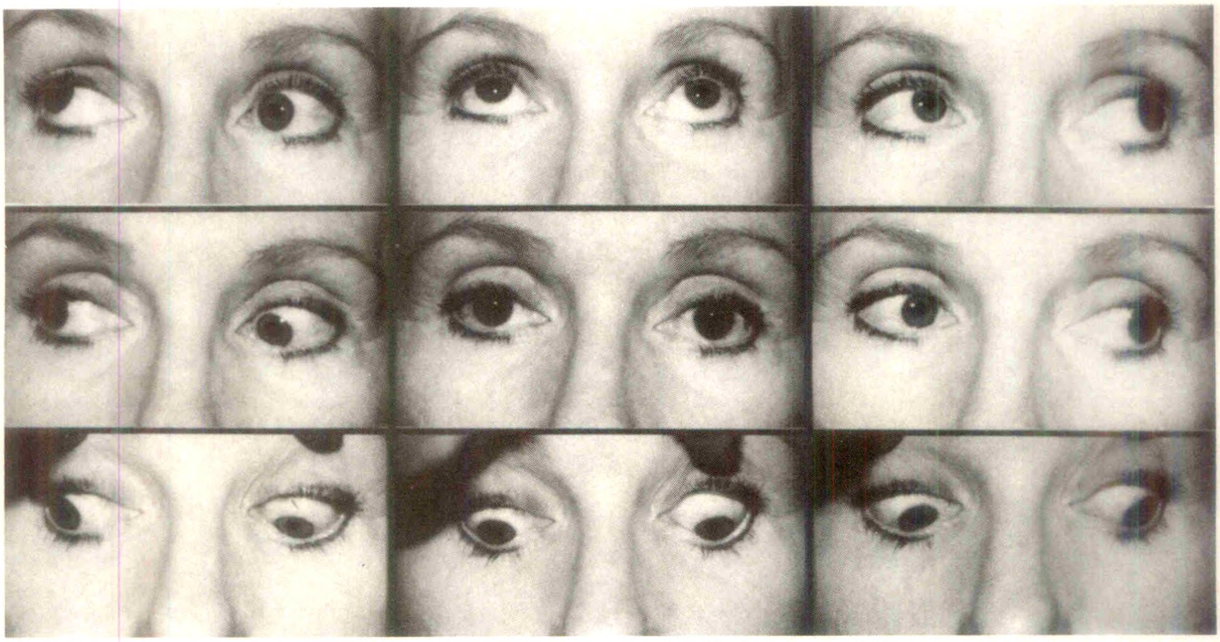


Figure (Erie). Ocular motility showing left acquired Brown's syndrome six months after peribulbar anesthesia.

arthritis or sinus disease. Acquired Brown's syndrome was diagnosed.

Peribulbar anesthesia, a local anesthetic that is injected outside the muscle cone, has been cited by proponents as having the advantages of greater ease of performance and a lower rate of complication.[3] In my case, however, presumably scarring within the trochlea and tendon sheath or perisheath scarring around the superior oblique tendon-sheath complex occurred secondary to the superonasal quadrant injection of anesthetic. Such scarring inhibits the free movement of the superior oblique's telescoping mechanism, thus restricting elevation of the globe in adduction.

Excellent anesthesia and akinesia without complications using peribulbar anesthesia that avoids the superonasal quadrant injection has been reported.[4] Use of this peribulbar technique should eliminate the risk of developing acquired Brown's syndrome.

References

1. Brown, H. W.: Congenital structural muscle anomalies. In Allen, J. H. (ed.): Strabismus Ophthalmologic Symposium I. St. Louis, C. V. Mosby, 1950, pp. 205–236.

2. ———: True and simulated superior oblique tendon sheath syndromes. Doc. Ophthalmol. 34:123, 1973.

3. Davis, D. B., and Mandel, M. R.: Posterior periocular anesthesia. An alternative to retrobulbar anesthesia. J. Cataract. Refract. Surg. 12:182, 1986.

4. Weiss, J. L., and Deichman, C. B.: A comparison of retrobulbar and periocular anesthesia for cataract surgery. Arch. Ophthalmol. 107:96, 1989.

Echography in the Diagnosis of Restrictive Motility Caused by Severe Myopia

Mark S. Ruttum, M.D., Mary Ann Lloyd, M.D., and Michael F. Lewandowski

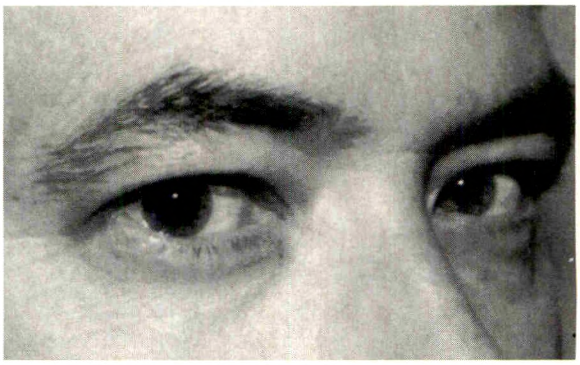
Department of Ophthalmology, Medical College of Wisconsin. This study was supported in part by an unrestricted grant from Research to Prevent Blindness, Inc.

Inquiries to Mark S. Ruttum, M.D., The Eye Institute, 8700 W. Wisconsin Ave., Milwaukee, WI 53226.

Demer and von Noorden[1] reported severe myopia as an unusual cause of restrictive ocular motility. Contact between the posterior globe and the orbital walls was suggested as the cause of such restriction on the basis of axial computed tomographic scans that showed globes that nearly filled the orbits. We treated a patient with this finding and used B-scan echography to confirm this mechanism of ocular motility restriction.

A 41-year-old man had a routine ocular examination as part of a comprehensive physical examination. He had had poor visual acuity in the right eye since early childhood. The only treatment for this problem had been spectacles. He otherwise had no ocular complaints, and he denied having diplopia.

Best-corrected visual acuity was R.E.: 20/400 with $-28.00 +5.00 \times 90$ degrees and L.E.: 20/20 with $-6.50 +1.75 \times 100$ degrees. There was 6 prism diopters of left hypertropia in primary position and mild limitation of abduction of the right eye (Fig. 1). Ocular rotations in other directions were normal. Ophthalmoscopy showed myopic changes of the posterior poles of both eyes and a posterior staphyloma of the right eye.



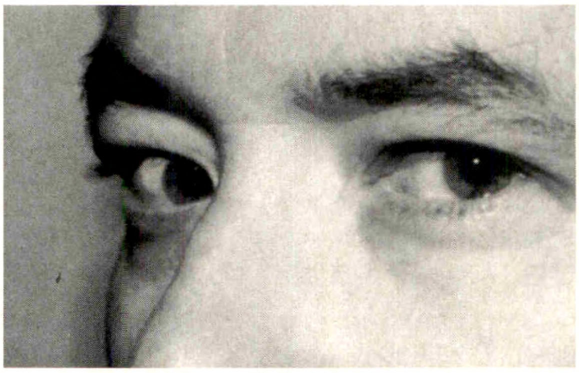


Fig. 1 (Ruttum, Lloyd, and Lewandowski). Ocular rotations showing mildly limited abduction of the right eye (top) in comparison with full abduction of the left eye (bottom).

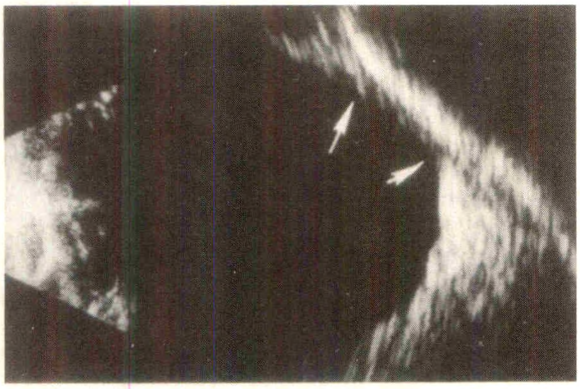


Fig. 2 (Ruttum, Lloyd, and Lewandowski). B-scan of abducted right eye showing flattening of posteromedial wall of globe (arrows) against medial orbital wall.

Thyroid function studies gave normal results. Saccadic velocities for horizontal gaze were normal and symmetric. A-scan echography showed axial lengths of 32.0 mm in the right eye and 25.6 mm in the left eye. The extraocular muscles were normal in size. B-scan echography demonstrated a conical posterior staphyloma in the right eye. Flattening of the posteromedial wall of the globe against the medial orbital wall occurred with abduction of the right eye (Fig. 2). No contact between the ocular and orbital walls was seen with gaze in other directions. The patient has not needed treatment for this motility disorder.

We have documented contact between the globe and an orbital wall in a patient with unilateral severe myopia that occurs only on gaze toward a direction in which limited ocular rotations can be seen on clinical examination. We agree, therefore, with Demer and von Noorden[1] that severe myopia can be a cause of restricted ocular motility because of this mechanical impediment to ocular movement. An alternative explanation for this restriction would be tightness in the medial rectus muscle itself, as reported by Hugonnier and Magnard[2] in severely myopic patients, but the absence of esotropia in primary position, as was seen in their patients, argues against this mechanism.

The degree of disproportion between the globe and orbit necessary for contact to occur between the globe and an orbital wall with ocular rotations is not known. A review of our echographic records disclosed only one other patient with this finding. The axial length in this patient's involved eye was 34.5 mm and contact also occurred with abduction. Information about ocular motility was not available.

Ophthalmic echography is a simple, noninvasive method of documenting globe-orbital wall contact as a cause of restricted ocular motility in the presence of severe myopia. Information about extraocular muscle size and acoustic texture can also be obtained with this technique to help rule out Graves' ophthalmopathy.[1,3]

References

1. Demer, J., and von Noorden, G.: High myopia as an unusual cause of restrictive motility disturbance. Surv. Ophthalmol. 33:281, 1989.

2. Hugonnier, R., and Magnard, P.: Les déséquilibres oculo-moteurs observés en cas de myopie forte. Ann. Oculist. 202:713, 1969.

3. Ossoinig, K. C.: Ultrasonic diagnosis of Graves' ophthalmopathy. In Gormon, C. A., Waller, R. R., and Dyer, J. A. (eds.): The Eye and Orbit in Thyroid Disease. New York, Raven Press, 1984, pp. 185–211.

Elimination of the Risk of Needle-Stick Injury in Handling Donor Eyes

Erik van Rens, M.D., and John W. Reed, M.D.

Department of Ophthalmology, Wake Forest University Medical Center.

Inquiries to John W. Reed, M.D., Department of Ophthalmology, Bowman Gray School of Medicine, 300 S. Hawthorne Rd., Winston-Salem, NC 27103.

When an eye becomes available for donation, a physician or other person trained in an enucleation technique removes the eye and prepares it for collection by the eye bank. During that preparation, the eye is positioned in a metal cage and secured by a sterile pin or needle placed through the stump of the optic nerve. The metal cage is then placed in a glass jar and irrigated with an antibiotic solution.[1]

After several incidents of needle-stick injury to the enucleator at our institution and at the North Carolina Eye and Human Tissue Bank while placing the needle through the optic nerve stump, we developed an alternative procedure for securing the optic nerve in the metal cage. With the increase in human immunodeficiency virus and hepatitis carriers, a needle-stick injury can be potentially harmful to the enucleator. A simple, inexpensive, metal test clamp, which can be obtained from any store having electronic parts, is placed on the optic

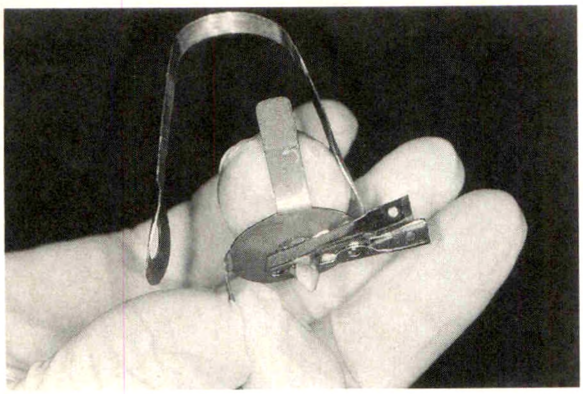


Figure (van Rens and Reed). Enucleated eye in metal cage, secured with metal clip on the optic nerve stump.

nerve once the eye is in the cage. There is no pin or needle to stick the enucleator, and the eye is prevented from moving in the glass jar and potentially damaging the corneal tissue (Figure). We now use this clamp with approval from the North Carolina Eye and Human Tissue Bank at Winston-Salem and have found it to be better than the previous method. Because the clamp does compress the optic nerve tissue, this method is not recommended for donor eyes that will be used for research on the optic nerve itself.

Reference

1. Gallagher, M. A.: Tissue removal. In Brightbill, F. S. (ed.): Corneal Surgery. Theory, Technique, and Tissue. St. Louis, C. V. Mosby, 1986, pp. 24–29.

Capnocytophaga Keratitis Associated With Poor Dentition and Human Immunodeficiency Virus Infection

Benjamin H. Ticho, M.D., Robert C. Urban, Jr., M.D., Marc J. Safran, M.D., and David D. Saggau, M.D.

Department of Ophthalmology, University of Illinois at Chicago Eye and Ear Infirmary.

Inquiries to Benjamin H. Ticho, M.D., University of Illinois at Chicago Eye and Ear Infirmary, 1855 W. Taylor St., Chicago, IL 60612.

Capnocytophaga, a fusiform gram-negative anaerobic bacterium, is a rare cause of microbial keratitis.[1-4] The organism is part of the normal human oral flora, but may become pathogenic in periodontitis and immunocompromised conditions. *Capnocytophaga* keratitis has been reported in association with trauma[1-3] and long-term topical corticosteroid usage.[4]

A pregnant 29-year-old woman had a three-day history of pain, photophobia, eyelid swelling, and decreased vision in the right eye. She denied any history of contact lens use, foreign body exposure, or recent ocular trauma. She admitted to daily cocaine and intravenous heroin abuse, as well as regular marijuana, tobacco, and alcohol use. Her history was further significant for prostitution and for hospitalization for hepatitis at age 17 years. The patient denied any history of sexually transmitted diseases or human immunodeficiency virus infection.

Visual acuity was R.E.: hand motions and L.E.: 20/30. Results of examination of the left eye were unremarkable. Examination of the right eye showed local eyelid and periorbital edema. The conjunctiva was markedly hyperemic. A 2.5 × 2.5-mm necrotic half-thickness, corneal ulcer was apparent in the superotemporal quadrant, along with a small adjacent satellite lesion (Figure). The nonulcerated cornea was edematous with marked superficial punctate fluorescein staining. The anterior chamber was deep with plasmoid aqueous and dense fibrous strands extending from the iris to the corneal endothelial surface. A 2-mm white

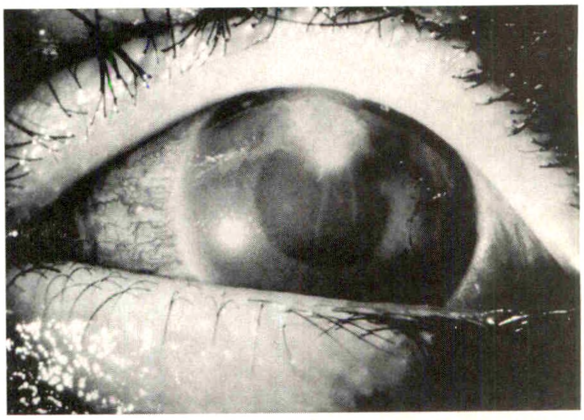


Figure (Ticho and associates). The right eye, three days after the onset of antimicrobial therapy for *Capnocytophaga* corneal ulcer, located in superotemporal quadrant, with fluffy, irregular borders and moderate surrounding haze.

hypopyon was apparent. The intraocular pressure was 13 mm Hg. The lens, vitreous, and fundus were unremarkable. A general physical examination disclosed poor oral hygiene with many carious teeth. Multiple skin lesions were consistent with longstanding intravenous drug abuse. The uterine fundus was balottable at 15 cm above the pubis. Generalized lymphadenopathy was absent.

Corneal scrapings showed numerous long, thin, gram-negative bacilli. Serum electrolytes and complete blood cell count were within normal limits. Serology for hepatitis B surface antigen and active syphilis (rapid plasma reagin) was negative. Urinalysis was positive for cocaine and opiates. Both enzyme-linked immunosorbent assay and Western blot testing for HIV infection were positive.

The patient was hospitalized and treated initially with topical fortified gentamicin sulfate (13.6 mg/ml) and cefazolin sodium (50 mg/ml) alternating every half hour, and atropine (1%) two times daily. The corneal scraping cultures became positive for *C. ochracea* four days later. The detection of this oral pathogen prompted the patient's referral to an oral surgeon and extraction of her carious teeth. Erythromycin ointment two times daily was substituted for the gentamicin. After 11 days of hospitalization, the ulcer had improved to a small persistent epithelial defect, and she was discharged. Manifest visual acuity was R.E.: 20/50 at follow-up examination three weeks later. The corneal infiltrate and anterior chamber reaction had largely cleared, leaving a superotemporal stromal scar with no overlying fluorescein staining.

Human immunodeficiency virus infection has multiple ocular manifestations, including infectious keratitis. Our patient had no other evidence of opportunistic infection. The role her concurrent poor dentition played in the development of the infectious keratitis is uncertain. Infection with *Capnocytophaga* is usually presumed to result from oral (gingival) contamination, although keratitis has been reported in an edentulous patient.[4] Antimicrobial treatment of *Capnocytophaga* keratitis has varied. Resistance to cephalosporins and aminoglycosides is common, and treatment with erythromycin, penicillin, ampicillin, and clindamycin has been recommended.[1-4] *Capnocytophaga* should be considered in the differential diagnosis in infectious keratitis in patients with a history of immunodeficiency or neutropenia, ocular trauma, and poor oral hygiene.

References

1. Roussel, T. J., Osata, M. S., and Wilhelmus, K. R.: *Capnocytophaga* keratitis. Br. J. Ophthalmol. 69:187, 1985.

2. Pamel, G. J., Buckley, D. J., Frucht, J., Krausz, H., and Feldman, S. T.: *Capnocytophaga* keratitis. Am. J. Ophthalmol. 107:193, 1989.

3. Heidemann, D. G., Pflugfelder, S. C., Kronish, J., Alfonso, E. C., Dunn, S. P., and Ullman, S.: Necrotizing keratitis caused by *Capnocytophaga ochracea*. Am. J. Ophthalmol. 105:655, 1988.

4. Ormerod, L. D., Foster, C. S., Paton, B. G., Haaf, J., and Baker, A. S.: Ocular *Capnocytophaga* infection in an edentulous immunocompetent host. Cornea 7:218, 1988.

IgA and Complement Immunofluorescent Pattern in Sebaceous Gland Carcinoma of the Eyelid

Hans E. Grossniklaus, M.D., Robert A. Swerlick, M.D., and Alvin R. Solomon, M.D.

Departments of Ophthalmology (H.E.G.), Pathology (H.E.G., A.R.S.), and Dermatology (R.A.S., A.R.S.), Emory University School of Medicine.

Inquiries to Hans E. Grossniklaus, M.D., L. F. Montgomery Eye Pathology Laboratory, Emory Eye Center, 1327 Clifton Rd. N.E., Atlanta, GA 30322.

Sebaceous gland carcinoma of the eyelid can clinically mimic cicatricial pemphigoid.[1] The immunofluorescence patterns in both conditions can be identical in some instances. We observed an eyelid biopsy specimen obtained from a patient clinically suspected to have cicatricial pemphigoid. Immunofluorescence showed a pattern consistent with cicatricial pemphigoid: however, histologic analysis disclosed sebaceous gland carcinoma.

A 77-year-old man had a one-year history of itching and mattering of the left eye. Examination showed best-corrected visual acuity of R.E.: 20/30 and L.E.: 20/40. The right eye contained a mild, nuclear sclerotic cataract. The upper tarsal plate of the left eye was thickened. The hyperemic left conjunctiva contained broad cicatricial bands across the palpebra superiorly and from the bulbar area to the cul-de-sac inferiorly. A nuclear sclerotic cataract was apparent. The clinical diagnosis was cicatricial

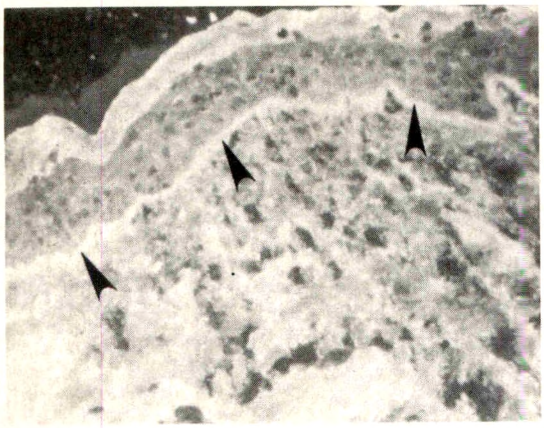


Fig. 1 (Grossniklaus, Swerlick, and Solomon). Direct immunofluorescence for IgA demonstrates linear pattern at the basement-membrane zone of the basal layer of the epithelium (arrowheads) (anti-human IgA, × 10).

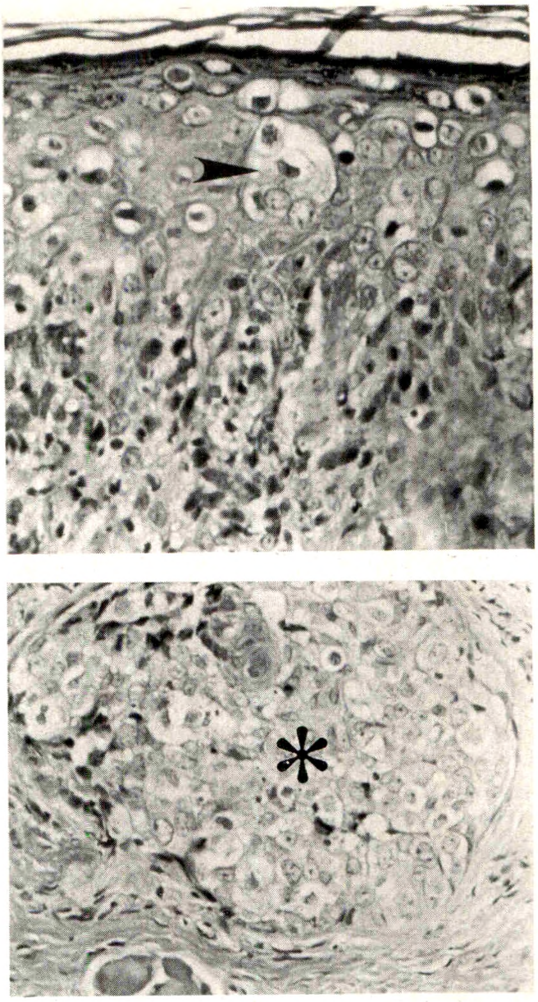


Fig. 2 (Grossniklaus, Swerlick, and Solomon). Top, The biopsy specimen contains pagetoid spread of sebaceous gland carcinoma cells (arrowhead) into overlying epithelium (hematoxylin and eosin, × 80). Bottom, Connective tissue underlying the epithelium contains a lobule of sebaceous gland carcinoma (asterisk) (hematoxylin and eosin, × 63).

pemphigoid. A biopsy specimen of the left lower eyelid, including an area of cicatricial change, was obtained. One half of the biopsy specimen was frozen in liquid nitrogen for immunofluorescence studies, and the other half was processed for light microscopy. Direct immunofluorescence showed an absence of staining for IgG and IgM but the presence of positive fluorescence for IgA and C3 in a linear pattern at the basement-membrane zone of the epithelium (Fig. 1). Histologic examination of the biopsy specimen showed lobules of sebaceous gland carcinoma with pagetoid spread of malignant cells into overlying epithelium (Fig. 2). A moderate infiltrate of mononuclear chronic inflammatory cells was apparent immediately subjacent to the epithelium.

An IgA and complement immunofluorescence pattern has been previously noted to occur in ocular cicatricial pemphigoid.[2] This pattern is not specific for cicatricial pemphigoid and has been seen in dermatitis herpetiformis among other conditions.[2] Our case adds sebaceous gland carcinoma with pagetoid spread to the list of conditions that can exhibit a linear IgA pattern at the basement-membrane zone of basilar epithelium. The subepithelial, mononuclear, chronic inflammatory cell infiltrate in our patient included numerous lymphocytes. Previous studies have shown the presence of T cells in association with ocular cicatricial pemphigoid[3] and sebaceous gland carcinoma of the eyelid.[4] It has been suggested that T cells may be effector cells responsible for an immunoregulatory defect that allows B-lymphocytes to produce autoantibodies, including IgA, to the basement-membrane zone of epithelium in ocular cicatricial pemphigoid.[3] A similar mechanism may have occurred in our case of sebaceous gland carcinoma.

References

1. Mashburn, M. A., Conkich, G. D., and Chase, D. R.: Meibomian gland adenocarcinoma of the eyelid with preauricular lymph node metastasis. Laryngoscope 95:1441, 1985.

2. Proia, A. D., Foulks, G. N., and Sanfilippo, F. P.: Ocular cicatricial pemphigoid with granular IgA and complement deposition. Arch. Ophthalmol. 103:1669, 1985.

3. Sacks, E. H., Jakobiec, F. A., Wieczorek, R., Donnenfeld, E., Perry, H., and Knowles, D. M.: Immunophenotypic analysis of the inflammatory infiltrate in ocular cicatricial pemphigoid. Further evidence for a T cell-mediated disease. Ophthalmology 96:236, 1989.

4. Herman, D. C., Chan, C.-C., Bartley, G. B., Nussenblatt, R. B., and Palestine, A. G.: Immunohistochemical staining of sebaceous cell carcinoma of the eyelid. Am. J. Ophthalmol. 107:127, 1989.

Retinoblastoma Associated With Holoprosencephaly

Vinay N. Desai, B.S.,
Carol L. Shields, M.D.,
Jerry A. Shields, M.D.,
Larry A. Donoso, M.D.,
and Rudolph S. Wagner, M.D.

Oncology Service (V.N.D., C.L.S., J.A.S.) and Retina Service (L.A.D.), Wills Eye Hospital and Jefferson Medical College of Thomas Jefferson University, and Department of Ophthalmology (R.S.W.), University of Medicine and Dentistry of New Jersey. This study was supported in part by the Ocular Oncology Fund of Wills Eye Hospital.

Inquiries to Jerry A. Shields, M.D., Wills Eye Hospital, 9th and Walnut Sts., Philadelphia, PA 19107.

Holoprosencephaly is a congenital defect associated with chromosome 13 in which the entire prosencephalon of the embryonic brain fails to divide properly into cerebral hemispheres, telencephalon and diencephalon, producing a single ventricle. We treated a patient with retinoblastoma, another chromosome 13 disorder, that occurred in association with holoprosencephaly.

A 30-month-old girl was referred to our institution for examination of leukocoria of the left eye. Her medical history showed semilobar holoprosencephaly, bilateral cleft lip and palate, and microcephaly (Figs. 1 and 2). At the age of 2 months, a fundoplication with feeding gastrostomy was performed to facilitate feeding and prevent aspiration. Anemia and thrombocytopenia developed at the age of 2 years. The patient had a history of seizures and electrolyte difficulties because of a pituitary gland abnormality. She was the product of a normal pregnancy, labor, and delivery. An older sister was normal. There was no family history of holoprosencephaly or retinoblastoma. Chromosomal analysis showed a normal karyotype.

Fig. 1 (Desai and associates). Photograph showing bilateral cleft lip and palate and microcephaly associated with semilobar holoprosencephaly.

Ocular examination showed bilateral wandering nystagmus. The anterior segment was normal in each eye. The right fundus was normal. Fundus examination of the left eye showed a total funnel-shaped retinal detachment with an inferior subretinal yellow-white mass extending from the 6 o'clock to the 9 o'clock meridians. The mass had prominent vascularity but clinical calcification was not seen. B-scan ultrasonography of the left eye demonstrated echodensities within the subretinal mass consistent with calcification. The clinical diagnosis was advanced unilateral sporadic retinoblastoma, and the affected left eye was enucleated. Gross examination of the sectioned eye showed a large, white, partially calcified intraocular mass with an overlying total retinal detachment (Fig. 3).

Microscopically, the tumor was composed of

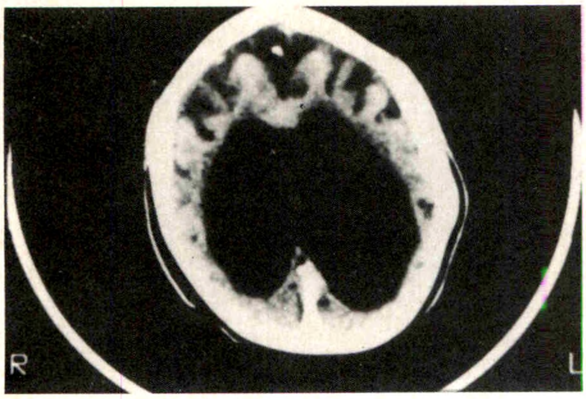


Fig. 2 (Desai and associates). Computed tomographic scan of the brain showing semilobar holoprosencephaly.

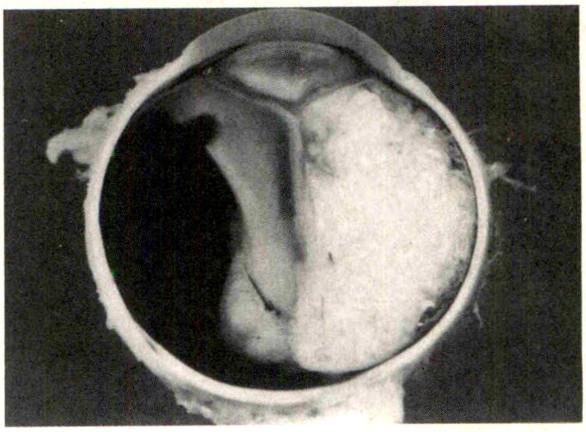


Fig. 3 (Desai and associates). Gross specimen showing retinoblastoma occupying inferior half of globe.

poorly differentiated neuroblastic cells with prominent basophilic nuclei and extensive areas of necrosis and calcification characteristic of retinoblastoma. No rosettes were identified. The optic nerve was invaded by the tumor to the level of the lamina cribrosa.

In most cases, the cause of holoprosencephaly is unknown. Environmental factors, maternal disease, and several chromosomal abnormalities have been associated with the disease. The most common chromosomal defects include trisomy 13, trisomy 18 (18 short arm deletion) syndrome, Meckel syndrome, Kallman syndrome, and autosomal dominant and recessive forms of holoprosencephaly.[1] The association of holoprosencephaly with 13q syndrome, a deletion of a portion of the long arm of chromosome 13, is well known.[2] The gene responsible for this disease, however, has not yet been identified.

The gene that predisposes patients to the development of retinoblastoma has been identified, cloned, and sequenced. It is large and highly complex, spanning over 200 Kb within the 1:4 band of the long arm of chromosome 13. Additional studies suggest that the gene is a recessive oncogene, that is, loss or inactivation of it at both alleles is required for the clinical development of retinoblastoma. One mechanism by which both alleles are inactivated involves chromosomal deletions at the 13q1:4 locus. Such deletions occur in approximately 5% of patients with retinoblastoma.[3] Our patient had a normal karyotype suggesting that any such 13q1:4 deletion would be small.

The frequencies of retinoblastoma and holoprosencephaly are 1:34,000 and 1:16,000 respectively.[1,3] Therefore, one would expect these two entities to occur together with an incidence of 1:5.44 × 10^8. In this case, the patient had a normal karyotype, which indicates a small deletion of chromosome 13 occurred and that the genes for retinoblastoma and holoprosencephaly are closely associated on chromosome 13.

References

1. Warkany, J., Lemire, R. J., and Cohen, M. M., Jr.: Mental Retardation and Congenital Malformations of the Central Nervous System. Chicago, Year Book Medical Publishers, Inc., 1981, pp. 370–375.
2. Allderdice, P. W., Davis, J. G., Miller, O. J., Klinger, H. P., Warburton, D., Miller, D. A., Allen, F. H., Jr., Abrams, C. A. L., and McGilvray, E.: The 13q-deletion syndrome. Am. J. Hum. Genet. 21:499, 1969.
3. Shields, J. A.: Diagnosis and Management of Intraocular Tumors. St. Louis, C. V. Mosby Co., 1983, pp. 437-496.

Floppy Eyelid Syndrome in a Child

Richard A. Eiferman, M.D., M. Douglas Gossman, M.D., Kelly O'Neill, M.D., and Craig H. Douglas, M.D.

Department of Ophthalmology, University of Louisville.

Inquiries to Richard A. Eiferman, M.D., 301 E. Muhammad Ali Blvd., Louisville, KY 40202.

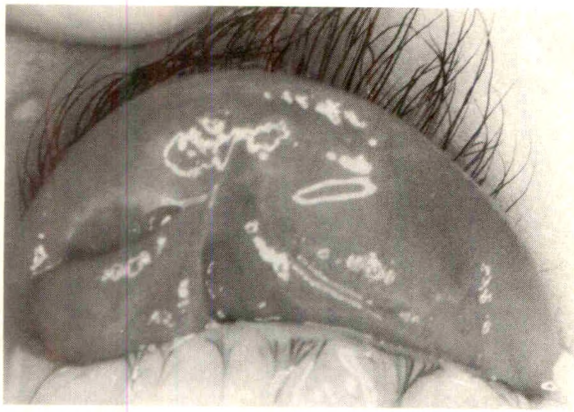


Fig. 1 (Eiferman and associates). Spontaneous eversion of right upper eyelid demonstrating severe induration and papillary response.

Spontaneous ectropion of the upper eyelid was described by Culbertson and Ostler[1] in obese men. There have been other cases reported in women[2] and in adults with hyperglycinemia.[3] We treated a child with this condition.

A 12-year-old boy was seen for severe chronic conjunctivitis of the right upper eyelid. He had a massive papillary reaction of the palpebral conjunctiva, a flaccid lateral canthal tendon and indurated tarsus that everted with slight upward traction (Figs. 1 and 2). A small punch biopsy showed chronic inflammation of the eyelid.

Treatment consisted of nonincisioned tarsorrhaphy for two months to allow the swelling to resolve. This was followed by horizontal shortening of the upper eyelid combined with lateral canthal tendon reconstruction. The patient had been followed up for six months postoperatively and has remained asymptomatic.

Spontaneous ectropion of the upper eyelid should be considered as part of the differential diagnosis of chronic conjunctivitis in children.

Fig. 2 (Eiferman and associates). Partial eversion of right upper eyelid and saddle nose.

References

1. Culbertson, W. W., and Ostler, H. B.: The floppy eyelid syndrome. Am. J. Ophthalmol. 92:568, 1981.
2. Moore, M. B., Harrington, J., and McCulley, J. P.: Floppy eyelid syndrome. Management including surgery. Ophthalmology 93:184, 1986.
3. Gerner, E. W., and Hughes, S. M.: Floppy eyelid with hyperglycinemia. Am. J. Ophthalmol. 98:614, 1984.

Presumed Sarcoid Choroidopathy Mimicking Birdshot Retinochoroidopathy

Roy D. Brod, M.D.

Department of Ophthalmology, Geisinger Medical Center.

Inquiries to Roy D. Brod, M.D., Department of Ophthalmology, Geisinger Medical Center, Danville, PA 17822.

Birdshot retinochoroidopathy is a specific posterior uveitis syndrome in which the diagnosis is based on the characteristic fundus appearance of flat depigmented choroidal lesions frequently concentrated nasal to the optic nerve.[1-3] Although it is thought to be a single nosologic entity, the cause remains unknown. I examined a patient with ocular findings consistent with birdshot retinochoroidopathy and biopsy-proven sarcoidosis. Sarcoidosis should be considered in the medical examination of patients with birdshot retinochoroidopathy.

A 44-year-old woman had a four-week history of blurred vision in her left eye. She had bilateral anterior uveitis, vitritis, and many yellow-fundus lesions, all of which were more progressive in the left eye. She also had mild disk edema in the left eye. A systemic evaluation disclosed hilar adenopathy on a chest X-ray and a subsequent transbronchial lymph node biopsy demonstrated noncaseating granulomatous inflammation consistent with sarcoidosis. She was treated with various combinations of oral, periocular, and topical corticosteroids for intermittent exacerbations of ocular inflammation over the following three years. Three years later, the patient was referred to my institution for retinal consultation because of progression of the fundus lesions.

Visual acuity was R.E.: 20/20 and L.E.: 20/

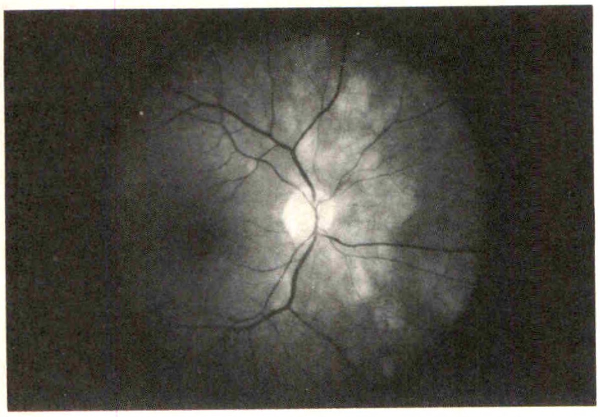


Fig. 1 (Brod). Fundus photograph of right eye showing optic nerve pallor and hypopigmented choroidal lesions concentrated nasal to the optic nerve.

40−2. Mild anterior chamber cells were apparent in the right eye and moderate anterior chamber cells in the left eye. No iris nodules were apparent. The right eye demonstrated mild posterior vitreous cell and the left eye had moderate posterior vitreous cell. Ophthalmoscopy of the right eye showed mild disk pallor, arteriolar narrowing, and multiple, flat, depigmented choroidal lesions concentrated nasal to the optic nerve and extending into the midperipheral fundus (Fig. 1). In the left eye, the patient had moderate disk pallor, arteriolar narrowing, cystoid macular edema, and multiple, depigmented, flat choroidal lesions scattered throughout the posterior and midperipheral fundus (Fig. 2). Although most of the spots were not visible on fluorescein angiography, some demonstrated mild late staining.

Color vision testing using the Farnsworth D-15 panel showed both eyes to be normal.

Fig. 2 (Brod). Fundus photograph of left eye demonstrating optic nerve pallor and numerous hypopigmented choroidal lesions.

Peripheral visual fields were constricted; the left eye more so than the right. Electroretinography showed minimally decreased amplitude for both scotopic and photopic responses in the right eye and moderately reduced amplitudes for both scotopic and photopic responses in the left eye. HLA-A29 antigen was not apparent.

Although there are numerous ocular manifestations of sarcoidosis, multiple depigmented choroidal lesions have rarely been reported.[4] Likewise, an extensive systemic evaluation for sarcoidosis has been infrequently performed in reported series of birdshot retinochoroidopathy cases.[3] Priem and Oosterhuis[3] sought a diagnosis of sarcoidosis in 38 of their 102 reported cases of birdshot retinochoroidopathy and identified one case of biopsy-proven sarcoidosis. A genetic predisposition to this disease is suggested by the high association with HLA-A29 antigen; however, the specific cause of birdshot retinochoroidopathy is unknown and may represent an ocular manifestation of several different pathogenic mechanisms.[3]

References

1. Ryan, S. J., and Maumenee, A. E.: Birdshot retinochoroidopathy. Am. J. Ophthalmol. 89:31, 1980.

2. Gass, J. D. M.: Vitiliginous chorioretinitis. Arch. Ophthalmol. 99:1778, 1981.

3. Priem, H. A., and Oosterhuis, J. A.: Birdshot chorioretinopathy. Clinical characteristics and evolution. Br. J. Ophthalmol. 72:646, 1988.

4. Spalton, D. J., and Sanders, M. D.: Fundus changes in histologically confirmed sarcoidosis. Br. J. Ophthalmol. 65:348, 1981.

Shadow- and Reflex-Free Use of Combined Fiberoptic Manipulators and Illuminators in Vitreous Surgery

Mark Michels, M.D., and Yossi Sidikaro, M.D.

Jules Stein Eye Institute, UCLA School of Medicine.

Inquiries to Yossi Sidikaro, M.D., 435 N. Roxbury Dr., Suite 410, Beverly Hills, CA 90210.

A primary concern of modern vitreoretinal surgery has been adequate visualization of the operative field. "Bright reflexes" occurring at "every optical interface" as described by Parel, Machemer, and Aumayr[1] prompted them to

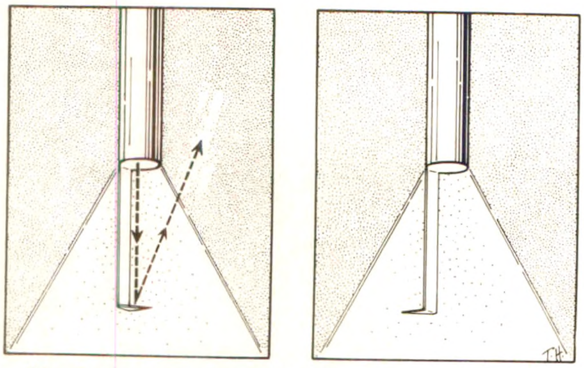


Fig. 1 (Michels and Sidikaro). Left, Arrow indicates reflected light and glare. Right, Glare is eliminated with pick directed away from instrument shaft.

develop a fiberoptic endoilluminator attachment for the vitreous infusion suction cutter. Machemer[2] also described peeling preretinal membranes with a hooked needle. Williams, Abrams, and Mieler[3] developed a series of illuminated retinal picks for vitreoretinal surgery using standard 20-gauge size and high quality fiberoptic illumination.

All of the instruments described by Williams, Abrams, and Mieler have an angulated pick device bent toward the light shaft. The developers noted that the tips of these instruments cast a small shadow and that by bending the proximal portion of the tip 20 to 30 degrees away from the longitudinal axis, the shadow is minimized while allowing effective tissue manipulation.[3] Ryan and Escoffery[4] also noted the prominent cannula shadow in the instruments they evaluated and offered a device with a pick that points in a direction that is tangential to the light pipe cylinder, which minimizes the shadow effect and allows for manipulation of tissues by either hooking or pushing.

We, too, have observed what has been reported but have additionally noted significant glare generated from the reflected light (Fig. 1, left). Even more important is that while dissecting epiretinal tissues, most fiberoptic-fitted picks illuminate the anterior surface of the dissected tissue rather than the posterior surface with its evolving tissue plane (Fig. 2, top). Not only is there glare and shadowing, but there is suboptimal illumination of the target tissue.

We have modified the existing illuminated picks so as to eliminate these problems. By bending the picks and other functional tips of these devices to an equal angle away from the shaft of the instrument, and by turning the shaft 180 degrees from the original working position, shadow and glare-free illumination is obtained directed precisely at the evolving tissue plane (Fig. 1, right, and Fig. 2, bottom). Using a needle holder and any of the currently used illuminated instruments, the modification is simple and easy to perform intraoperatively.

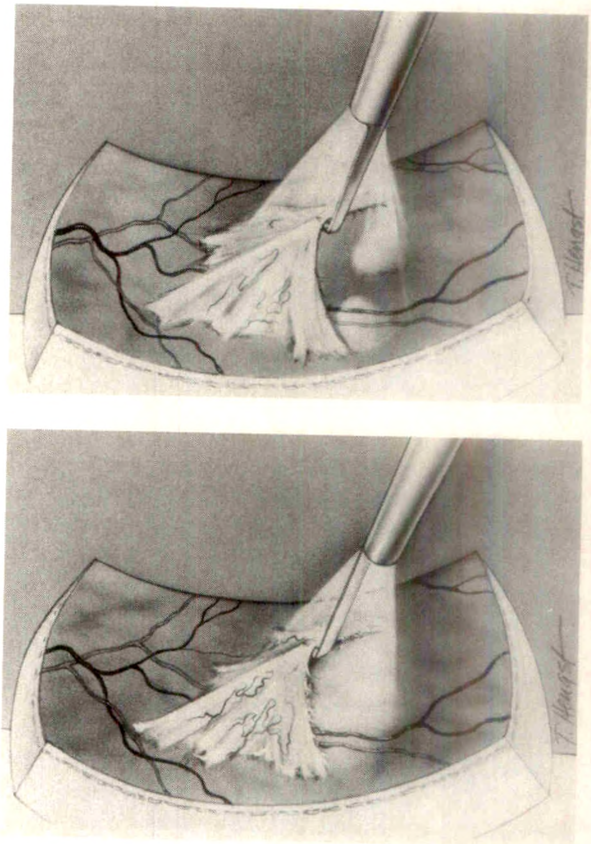


Fig. 2 (Michels and Sidikaro). Top, Most of illumination is directed away from evolving tissue plane. Available light is shadowed. Bottom, Most of illumination is now directed to evolving tissue plane without reflection or shadow.

This modification has allowed us to eliminate completely many of the annoying reflexes and shadows we encountered with existing devices. The modification is unique because it permits more complete visualization of the tissue planes of interest.

References

1. Parel, J.-M., Machemer, R., and Aumayr, W.: A new concept for vitreous surgery 4. Improvements in instrumentation and illumination. Am. J. Ophthalmol. 77:6, 1974.

2. Machemer, R.: A new concept for vitreous surgery 7. Two instrument techniques in pars plana vitrectomy. Arch. Ophthalmol. 92:407, 1974.

3. Williams, G. A., Abrams, G. W., and Mieler, W. F.: Illuminated retinal picks for vitreous surgery. Arch. Ophthalmol. 107:1086, 1989.

4. Ryan, E. H., and Escoffrey, R. F.: A modified illuminated membrane pick. Retina 9:77, 1989.

A New Instrument for Ab Interno Drainage of Subretinal Fluid

Mark Michels, M.D., and Yossi Sidikaro, M.D.

Jules Stein Eye Institute, UCLA School of Medicine.

Inquiries to Yossi Sidikaro, M.D., 435 N. Roxbury Dr., Suite 410, Beverly Hills, CA 90201.

Internal drainage of subretinal fluid was first utilized by Cibis[1] in the context of scleral buckling surgery. Charles[2] was the first to apply the principle of internal exchange of gas with subretinal fluid using modern vitrectomy techniques and the flute needle and later using the tapered extrusion needle. There have been numerous modifications of this technique including reflux features for incarcerated retina[3] and more controlled egress of fluid.[2] Flynn and associates[4] have developed a retractable, flexible, cannulated extrusion device to facilitate subretinal fluid aspiration.

Some of the persistent difficulties associated with all widely used extrusion devices is retinal incarceration in the extrusion port and inadvertent damage to the underlying retinal pigment epithelium and choroid (Fig. 1, top left and right). McDonald and associates[5] suggested that the drainage instrument be kept just above or at the plane of the retinotomy during the last stages of the fluid-gas exchange to prevent damage. They further acknowledged that suboptimal visualization may preclude precise instrument tip localization.

Our new device, the guarded port extrusion needle, largely eliminates the difficulties described above. The device is fitted to a standard 20-gauge shaft. The unique tip consists of a 27-gauge extension of the 20-gauge shaft that is bent 90 degrees from the extended shaft for a distance of 1.5 mm. The extrusion port is on the underside of the right angle extension (Fig. 1, bottom left).

The tip design allows placement of the right-angle tip under the edge of the retina at the drainage site with gentle tenting of the retina in this location. Because the extrusion port is on the opposite side of the retina, the retina can be draped or tented over the instrument and retinal incarceration does not occur. The slightly tented configuration permits elevation of the retina and safe placement of the instrument away from the underlying retinal pigment epi-

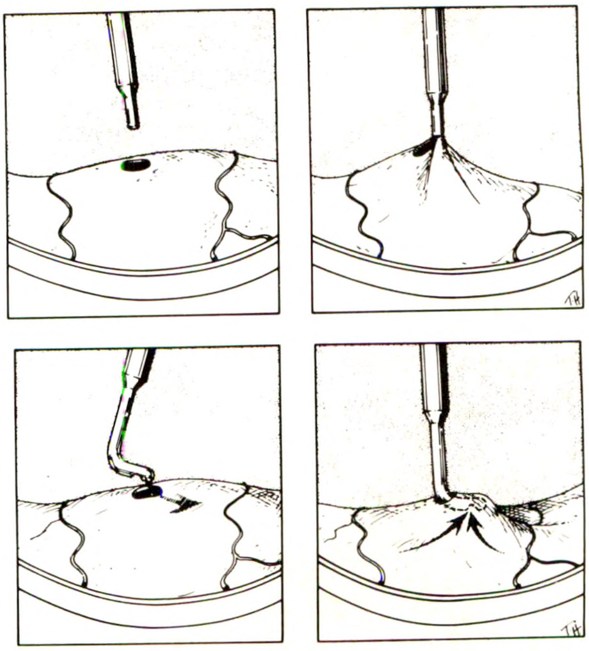


Fig. 1 (Michels and Sidikaro). Top, left and right, Retina is easily incarcerated with popular extrusion device. Bottom left, Guarded port needle extrusion port is on underside, away from overlying retina. Bottom right, Guarded port needle tents retina safely away from underlying retinal pigment epithelium, choroid, and overlying retina.

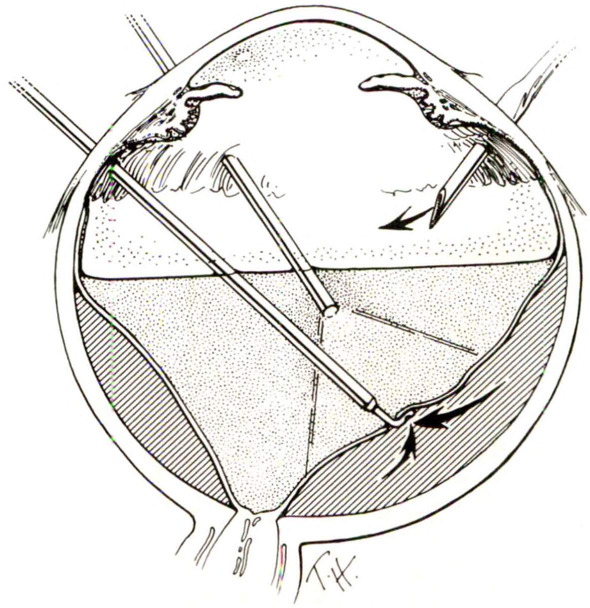


Fig. 2 (Michels and Sidikaro). Demonstrates use of the guarded port extrusion needle.

thelium and choroid while facilitating continued aspiration of subretinal fluid even during the last stages of the fluid-gas exchange (Fig. 1, bottom right). The draping effect also provides visual clues as to tip location during stages when visualization is difficult (Fig. 2).

We have successfully used this instrument in over 100 cases at our institution without complication. While other extrusion devices are available, we have found the guarded port needle to be particularly useful and safe.

References

1. Cibis, P. A.: Vitreoretinal Pathology and Surgery in Retinal Detachment. St. Louis, C. V. Mosby, 1965, p. 89.
2. Charles, S.: Vitreous Microsurgery, ed. 2. Baltimore, Williams & Wilkins, 1987, p. 89.
3. Zivojnovic, R., and Vijfvinkel, G. J.: A modified flute needle. Am. J. Ophthalmol. 96:548, 1983.
4. Flynn, H. W., Jr., Blumenkranz, M. S., Parel, J. M., and Lee, W. G.: Cannulated subretinal fluid aspiration for vitreoretinal microsurgery. Am. J. Ophthalmol. 103:106, 1987.
5. McDonald, H. R., Lewis, H., Aaberg, T. M., and Abrams, G. W.: Complications of endodrainage retinotomies created during vitreous surgery for complicated retinal detachments. Ophthalmology 96:358, 1989.

Correspondence

Glaucomalike Disks Without Increased Intraocular Pressure or Visual Field Loss

EDITOR:

The article "Glaucomalike disks without increased intraocular pressure or visual field loss," by G. Tomita, T. Takamoto, and B. Schwartz (Am. J. Ophthalmol. 108:496, November 1989) increases our knowledge of physiologic cups. I was confused, however, by the choice of units of measure in Table 4. In the Subjects and Methods section, the authors used cup parameters of volume, area, depth, and slope, expressed as a ratio to the disk area × 100 (%), except cup slope, which was expressed in degrees.

According to a standard mathematics text,[1] percentage is a unitless expression that can only be invoked when the numerator and denominator are expressed in like units of measure. For example, cup area/disk area (expressed in mm^2/mm^2 or $\mu m^2/\mu m^2$) is unitless, and may be expressed as the decimal ratio or as the percentage (ratio × 100%). However, in Table 4, cup volume/disk area ($mm^3/mm^2 =$ mm) is not unitless, and must be expressed in mm (or μm), not as a percentage. Likewise, cup depth/disk area ($mm/mm^2 = mm^{-1}$) cannot be a percentage, but rather must be expressed in mm^{-1} (or μm^{-1}). I am interested to learn how the authors derived percentages from these units of measure.

JEFFREY W. KALENAK, M.D.
Cleveland, Ohio

Reference

1. Riddle, D. F.: Calculus and Analytic Geometry. Belmont, California, Wadsworth Publishing Co., 1970, p. 136.

Reply

EDITOR:

Dr. Kalenak brings up two issues: the final units that should be attributed to the ratios or percentages for cup parameters/disk area, and the use of a ratio or percentage. He is correct in his comments regarding units of measure for Table 4. Cup volume and cup depth are not unitless. The unit for cup volume ratio is mm and for cup depth ratio is mm^{-1}.

We chose the disk area as the reference to minimize variation of magnification with the taking of photographs. Therefore, we can express our measurements as a ratio or as a percentage that is the ratio of cup parameter/disk area × 100. This is only a convenience to express and compare the data among the different diagnostic groups.

GOJI TOMITA, M.D.
TAKENORI TAKAMOTO, PH.D.
BERNARD SCHWARTZ, M.D.
Boston, Massachusetts

Pars Plana Vitrectomy in the Management of Dislocated Posterior Chamber Lenses

EDITOR:

In the article "Pars plana vitrectomy in the management of dislocated posterior chamber lenses," by R. V. Campo, K. D. Chung, and R. T. Oyakawa (Am. J. Ophthalmol. 108:529, November 1989), the authors described a technique for transsclerally fixating a dislocated posterior chamber intraocular lens without capsular support. We developed a new needle for the placement of iris fixation sutures that we believe would greatly simplify the placement of the transscleral suture at the time of vitrectomy. The instrument is a 27-gauge needle with a 7/1,000-inch drill hole centered in the midportion of the needle bevel to allow passage of the suture material. This instrument, currently available from Trek Medical Products, would facilitate the rapid placement of the transscleral suture.

We do have some concern regarding the reported technique and the associated stability of the transsclerally fixated haptic. Recently, Apple and associates[1] reported on the histopathologic findings in four cases of transsclerally fixated posterior chamber intraocular lenses. Only one of the eight haptics was actually located in the ciliary sulcus. Apple and associates postulated that the transscleral suture itself may be responsible for maintaining anatomic positioning of the lens.

We treated a patient with a secondary transsclerally fixated posterior chamber intraocular lens placed after postcataract traumatic primary posterior lens expulsion. This patient had traumatic iris disinsertion allowing direct visualization of the ciliary sulcus. In this patient, both lens haptics were posterior to the ciliary sulcus and the haptics appeared to be supported by the suture itself, in agreement with the postmorten findings of Apple and associates.

This observation suggests the importance of a direct physical attachment between the transscleral suture and the haptic of the posterior chamber intraocular lens. This is the technique currently advocated by Stark and associates[2] and Spigelman and associates[3] in the anterior segment approach to transscleral lens fixation. This may remain only a theoretical concern, but we believe the question of haptic stability in the pars plana approach warrants further investigation.

TIMOTHY G. MURRAY, M.D.
GARY W. ABRAMS, M.D.
Milwaukee, Wisconsin
JOHN STANLEY, M.D.
San Francisco, California

References

1. Apple, D. J., Price, F. W., Gwin, T., Imkamp, E., Daun, M., Casanova, R., Hansen, S., and Carlson, A. N.: Sutured retropupillary posterior chamber intraocular lenses for exchange or secondary implantation. Ophthalmology 96:1241, 1989.
2. Stark, W. J., Goodman, G., Goodman, D., and Gottsch, J.: Posterior chamber intraocular lens implantation in the absence of posterior capsular support. Ophthalmic Surg. 19:240, 1988.
3. Spigelman, A. V., Lindstrom, R. L., Nichols, S. D., Lindquist, T. D., and Lane, S. S.: Implantation of a posterior chamber lens without capsular support during penetrating keratoplasty or as a secondary lens implant. Ophthalmic Surg. 19:396, 1988.

Reply

EDITOR:

We thank Drs. Murray, Abrams, and Stanley for their comments regarding our article and for bringing to our attention their new 27-gauge sewing needle. We anxiously await the opportunity to evaluate this device, and we share their optimism regarding its applicability to our transscleral haptic suturing method.

RANDY V. CAMPO, M.D.
KELLY D. CHUNG, M.D.
RAY T. OYAKAWA, M.D.
Phoenix, Arizona

Automated Perimetry, Tonometry, and Questionnaire in Glaucoma Screening

EDITOR:

In the article "Automated perimetry, tonometry, and questionnaire in glaucoma screening," by T. K. Mundorf, T. J. Zimmerman, G. F. Nardin, and K. S. Kendall (Am. J. Ophthalmol. 108:505, November

1989), the authors applied several potential screening techniques for the identification of glaucoma. No practical, single test exists that is sensitive, specific, and efficient in distinguishing normal individuals from those who have established glaucomatous optic nerve damage or are at particularly high risk for such damage. In their study, the authors included the combination of intraocular pressure, suprathreshold perimetry, and a weighted questionnaire consisting of potential risk factors. As they point out, the results were less than ideal. Nonetheless some of the criteria they chose as screening cutoffs deserve additional discussion.

Psychophysical testing will remain the benchmark criterion for some time to come, since it definitively assesses optic nerve function. We still must choose an ideal, or at least optimal strategy. The authors used the three-zone full field strategy. They considered four or more abnormal defects (relative or absolute reductions in threshold) in any single quadrant as abnormal. Kosoko, Auer, and I previously evaluated a similar screening strategy.[1] Our results indicated that almost all information could be identified from the nasal hemisphere alone, thereby potentially reducing the number of points that needed to be tested. The test could be further shortened by only using a two-zone strategy (not bothering to retest depressions at greater intensity) since retesting yielded no additional information. The full, unmodified test required an average of 9.3 ± 1.7 minutes among normal patients and glaucoma suspects (ranging from 8.6 minutes in the youngest group to 11.4 minutes in the oldest) and 14.1 ± 3.2 minutes among glaucoma patients.[2] Finally, in our experience, the appropriate criterion for abnormality was 17 defects, which provided a better balance between sensitivity and specificity (96% and 83%, respectively)[1] than the cutoff used by Mundorf and associates.

It may not be clear to the reader that the 20% sensitivity (identification rate of true positives) by tonometry alone, a much lower rate than usually reported, is related to their choice of a screening criterion of 24 mm Hg or higher. The usual cutoff, 21 mm Hg or higher, would no doubt yield a higher sensitivity but also a lower specificity.

The use of a screening questionnaire is imaginative, even if the results were disappointing. It is possible that more comprehensive data now being collected and analyzed in larger prevalence and longitudinal studies will result in refined questions and weighting factors that will improve the sensitivity and specificity of this technique.

ALFRED SOMMER, M.D.
Baltimore, Maryland

References

1. Kosoko, O., Sommer, A., and Auer, C.: Screening with automated perimetry using a threshold-related three-level algorithm. Ophthalmology 93:882, 1986.

2. ———: Duration of automated suprathreshold vs. quantitative threshold field examination. Arch. Ophthalmol. 104:398, 1986.

BOOK REVIEWS

Edited by H. Stanley Thompson, M.D.

A Color Atlas of Ptosis. A Practical Guide to Evaluation and Management. By Jonathan J. Dutton. Singapore, P. G. Publishing, 1989. 156 pages, index, illustrated. $100

Reviewed by JOHN A. LONG
Birmingham, Alabama

The surgical management of blepharoptosis is discussed in a clear and easily readable format in this well-illustrated text. The book provides the reader with easy to follow, step-by-step instructions on how to perform basic blepharoptosis surgery. This single-author book is designed for the occasional blepharoptosis surgeon who may wish to review a surgical procedure before beginning an operation.

The book has seven short chapters. The first half of the book is divided into three chapters covering the classification of blepharoptosis, the surgical anatomy of the eyelids, and the examination of the patient with blepharoptosis. A collection of photographs illustrates many of the common types of blepharoptosis. The chapter on eyelid anatomy is illustrated with detailed color drawings outlining essential anatomic features.

The second half of the book consists of four chapters outlining four different surgical approaches to blepharoptosis. The techniques included are the Fasanella-Servat procedure, levator aponeurosis surgery, levator resection, and frontalis suspension. A short list of references at the end of each chapter includes landmark articles describing each of the techniques.

The four surgical approaches to blepharoptosis surgery are described in the text. Each technique is illustrated with quality color photographs and corresponding line drawings that allow the reader to visualize the details of each procedure. After the description of each surgical technique there is a brief discussion of the management of common complications.

The author clearly achieves the goal of the book, which is to provide the occasional blepharoptosis surgeon with a simple guide to surgery. Each of the techniques is widely used and has withstood the test of time. Most patients with blepharoptosis can be adequately treated with the techniques illustrated in this book. This book belongs on the shelf of every ophthalmologist and eyelid surgeon who treats blepharoptosis.

Oculoplastic and Orbital Emergencies. Edited by John V. Linberg. Norwalk, Connecticut, Appleton & Lange, 1990. 237 pages, index, illustrated. $39.95

Reviewed by GARY S. WEINSTEIN
Pittsburgh, Pennsylvania

This concise, well-written text on emergencies involving the ocular adnexa and orbit contains a series of clearly indexed algorithms or flow charts, which allows the reader to arrive rapidly at a differential diagnosis when confronted with an emergency. "Core references" are listed in boldface at the end of each chapter to allow easy access to the most important up-to-date references. Surgical techniques and lists of antibiotics with dosages are given to facilitate a treatment plan.

Periorbital trauma is covered in chapters on eyelid and canthal lacerations, canalicular lacerations, periorbital animal bites, acute eyelid and periocular burns, blowout fractures, zygomatic and complex facial fractures, orbital foreign bodies, and traumatic optic neuropathies. A wide spectrum of orbital emergencies are discussed in chapters on preseptal and orbital cellulitis and abscess, acute proptosis in children and adults, orbital apex syndrome, orbital hemorrhage, and dacryoadenitis. The list of emergencies is completed with chapters on chalazia and hordeolum and acute dacryocystitis.

Although finding information using the table of contents and index is easy, organizing the chapters under trauma and orbital emergency sections would facilitate the text. For example, the first two chapters cover eyelid and canalicular lacerations, and the last chapter reviews periorbital animal bites. The chapter on eyelid laceration states that passing a full-thickness suture through the lower eyelid tarsus is permissible, although this could lead to significant corneal irritation. The chapter on canalicular lacerations recommends an ethmoidal block rather than infiltrative anesthesia for repair under local anesthesia. A regional block is usually unnecessary and increases the risk of hematoma formation if the anterior ethmoidal artery is encountered. The management algorithm in this chapter lists not repairing the canaliculus as a possible option, although most oculoplastic surgeons, including the author of

the chapter, believe that all lacerated canaliculi should be repaired. The chapter on burns, which contains several case histories, should be expanded to include specific treatment guidelines.

The overall quality of the text and illustrations is excellent. Each chapter has a great deal of useful information to help the physician develop a good differential diagnosis and treatment plan. The chapter on zygomatic and complex facial fractures discusses material not usually available in standard ophthalmic textbooks. This book belongs on the bookshelf of every physician treating these problems and in every ophthalmic emergency room.

Myopia Surgery. Anterior and Posterior Segments. Edited by Frank B. Thompson. New York, Macmillan Publishing Co., Inc., 1990. 338 pages, index, illustrated. $95

Reviewed by MARK J. MANNIS
Sacramento, California

Every ophthalmic surgeon is confronted with the myopic patient and must deal with the special refractive and surgical considerations that are associated with the myopic eye. This multi-authored volume is a collection of essays by well-known anterior and posterior segment surgeons. The book consists of 11 chapters divided into three sections. The first section is a single chapter that discusses the pathogenesis and pathophysiology of the myopias. The second section, consisting of seven chapters, concerns surgical therapy of myopia including radial keratotomy, epikeratophakia, lensectomy, and myopic keratomileusis. The chapters on these subjects are followed by a round-table discussion format in which the authors elaborate on some of the controversies and questions regarding these newer procedures. The final chapter in this section deals with special considerations for the ophthalmologist performing cataract surgery on the myopic individual. The third section of the book deals with posterior segment surgery in myopia and includes discussions of vitrectomy, retinal detachment surgery, and scleral reinforcement procedures in the severely myopic eye.

This book is unique as a compendium of surgical approaches specifically for the myopic eye. It contains information on most of the newer refractive procedures for myopia and additionally provides the reader with a source of useful tips relevant to standard surgery performed on the myopic individual.

The text is flawed in some ways. As a multi-authored volume it suffers from a multiplicity of styles. This is particularly evident in the second section of the book dealing primarily with refractive surgery. The reader must repeatedly ascertain whether the conclusions are based on scientific data or personal surgical experience. In general, the illustrations in the book are of good quality, and there is a large selection of photographs, diagrams, and charts. Unfortunately, the color plates dealing with a diversity of subjects are all grouped together in the middle of the book rather than being in the context of the individual chapters.

These minor flaws notwithstanding, Myopia Surgery is a definite contribution to the modern ophthalmic library and will be of use to the anterior segment and refractive surgeon, the general ophthalmologist, and the posterior segment surgeon alike. It provides a convincing case for the uniqueness of myopia as a surgical problem.

Developments in Ophthalmology, vol. 20. Graves' Ophthalmopathy. Developments on Diagnostic Methods and Therapeutical Procedures. Edited by C. Renate Pickardt and Klaus Peter Boergen. Basel, Switzerland, Karger, 1989. 230 pages, index, illustrated. $130

Reviewed by STEVEN E. FELDON
Los Angeles, California

This text comprises the proceedings of the International Workshop, Homburg/Sarr, held on Oct. 7, 1987, and documents the first interdisciplinary conference on this important subject. Original research topics are interspersed with cogent reviews on pathogenetic aspects, diagnostic procedures, medical treatment, radiotherapy, and surgical treatment. Almost all of the chapters are well written and many are also well illustrated.

Beyond the acknowledgment that Graves' ophthalmopathy is an autoimmune disease closely associated with Graves' hyperthyroidism, there is little agreement regarding cause, diagnosis, or management. This apparent lack of cohesion should not be construed as a weakness, but as being consistent with the editors'

"aim to stimulate a closer interdisciplinary cooperation between all those who are concerned with diagnosis and treatment of patients with Graves' ophthalmopathy."

A major accomplishment of this text is an overall perspective of the immunologic basis of Graves' ophthalmopathy. Evidence for the existence of extraocular muscle antibodies and for the existence of cross-reactivity between thyroid and orbital antigens is thoughtfully examined and critically discussed. The degree of methodologic detail is convincing, but is not overwhelming to the uninitiated.

Of special interest to ophthalmologists are chapters on ultrasonography, computed tomography, and magnetic resonance imaging of the orbit. In their review of computed tomography and magnetic resonance imaging, Markl, Hilbertz, and Mann from Munich report the radiologic characteristics of fatty degeneration, edema, and fibrosis of the extraocular muscles in Graves' ophthalmopathy. Also of interest is an impressive number of clinical trials describing new and standard therapies. The merits of corticosteroids, cyclosporine, plasma exchange, ciamexon (2-cyan-aziridine), Venalot (coumarin and troxerutin), orbital irradiation, and orbital decompression are discussed.

The information in this book is both intriguing and frustrating for the endocrinologist as well as the ophthalmologist. Some of it is contradictory and none of it is sufficient to formulate a rational understanding of either the disease process or the management of Graves' ophthalmopathy. This viewpoint is shared by Dr. Robert Volpé from the University of Toronto who summarized the proceedings. His call for "multicentered, randomized, prospective double blind control studies for therapeutic trials" and for "world-wide standards of precise and objective clinical measurements" are critical to progress in controlling this disorder.

Books Received

Accountability in Research. Policies and Quality Assurance. Edited by Adil E. Shamoo. New York, Gordon and Breach, 1989. Softcover, 83 pages. $56

This is a new quarterly journal devoted to the critical examination of issues involving the integrity of scientific data. It hopes to be a forum for the development of new policies, procedures, and standards for acquiring, analyzing, and auditing data.

Atlas of Ocular Motility. By Leonard B. Nelson and Robert A. Catalano. Philadelphia, W. B. Saunders Company, 1989. 240 pages, index, illustrated. $85

This manual and atlas is designed to instruct ophthalmology residents in strabismus. The photographs have a casual look that intrudes on the subject matter; it will probably be improved in the next edition.

Developments in Ophthalmology. Ultrastructure of the Conjunctival Epithelium. By Klaus-Peter Steuhl. Basel, Karger, 1989. 104 pages, index, illustrated. $64

A monograph on the structure of the five cell types found in the human conjunctival epithelium and how these are changed by dry eyes, lime burns, beta blockers, and the like.

Differential Diagnosis of Hereditary Vitreoretinopathy. By A. Spallone. Milan, Fogliazza Editore, 1989. 106 pages, index, illustrated. $70

A thoughtful and well illustrated monograph by an author who has studied the various hereditary vitreoretinal conditions for many years.

Inherited and Environmentally Induced Retinal Degenerations. Edited by Matthew M. LaVail, Robert E. Anderson, and Joe G. Hollyfield. New York, Alan R. Liss, Inc., 1989. 727 pages, index, illustrated. $150

This substantial volume contains the papers delivered at the International Symposium on Retinal Degenerations held in San Francisco in September 1988, together with a number of

papers contributed by people who could not attend the meeting.

Introduction to Ophthalmology, ed. 3. By John Parr. Oxford, Oxford University Press, 1989. Softcover, 233 pages, index, illustrated. $35

This is a better than average general ophthalmology text for medical students. Professor Parr keeps it simple and direct, and the illustrator, Peter Scott, deserves credit for the unusually clear drawings.

Manual of Retinal Surgery. Edited by Andrew J. Packer. New York, Churchill Livingstone, Inc., 1989. Softcover, 126 pages, index, illustrated. $39

This is a good starting point for the ophthalmology resident about to learn about surgery of the retina.

Microsurgery of the Eye. Main Aspects. Edited by S. N. Fyodorov. Commack, New York, Nova Science Publishers, Inc., 1987. 280 pages, index, illustrated. $75

Soviet anterior segment surgery is eerily similar to our own, and Fyodorov's group is vigorous and constantly trying new approaches. American anterior segment surgeons should find this book fascinating and will probably pick up some good ideas from it.

Vision and the Brain. The Organization of the Central Visual System. Edited by Bernard Cohen and Ivan Bodis-Wollner. New York, Raven Press, 1989. 364 pages, index, illustrated. $125

This carefully edited volume is No. 67 in a series of research publications sponsored by the Association for Research in Nervous and Mental Disease. Many of the 18 chapters contain important reviews. The editors have written a thoughtful preface, making this more than an ordinary conference proceedings.

The Visual Fields. Text and Atlas of Clinical Perimetry, ed. 6. By David O. Harrington and Michael V. Drake. St. Louis, C. V. Mosby, 1990. 405 pages, index, illustrated. $53.95

A slim, updated edition of an old standby. Some fields from an automated perimeter have been added.

The Book List

Diabetic Retinopathy. By Howard Schatz and H. Richard McDonald. San Francisco, The Retina Research Fund, 1988. Softcover, 71 pages, illustrated. $4

New Methods of Sensory Visual Testing. Edited by Michael Wall and Alfredo A. Sadun. New York, Springer-Verlag, 1989. 137 pages, index, illustrated. $49.95

Macular Degeneration. By Howard Schatz and H. Richard McDonald. San Francisco, The Retina Research Fund, 1987. Softcover, 51 pages, illustrated. $4

Proliferative Vitreoretinopathy. Edited by K. Heimann and P. Wiedemann. Heidelberg, Germany, Kaden Verlag, 1989. Softcover, 327 pages, illustrated.

Retinal Detachment and Vitreous Surgery. By H. Richard McDonald, Howard Schatz, and Robert N. Johnson. San Francisco, The Retina Research Fund, 1989. Softcover, 67 pages, illustrated. $4

Seeing Contour and Colour. Edited by J. J. Kulikowski, C. M. Dickinson, and I. J. Murray. Oxford, Pergamon Press, 1989. 818 pages, index, illustrated. $270

Sensory Systems I. Vision and Visual Systems. Edited by Richard Held. Boston, Birkhauser, 1988. Softcover, 133 pages, illustrated. $24.50

Strabismus Surgery. Oblique Procedures. By Ronald L. Price. San Francisco, American Academy of Ophthalmology, 1988. Videotape.

Strabismus Surgery. Rectus Recession and Resection. By Ronald L. Price. San Francisco,

American Academy of Ophthalmology, 1988. Videotape.

Surgery of the Eyelids and Orbit. An Anatomical Approach. By Bradley N. Lemke and Robert C. Della Rocca. Norwalk, Connecticut, Appleton & Lange, 1990. 332 pages, index, illustrated. $150

The Vitreous. Structure, Function, and Pathobiology. By J. Sebag. New York, Springer-Verlag, 1989. 173 pages, index, illustrated. $69

Meetings

Ocular Microbiology and Immunology Group: 23rd Annual Meeting

The 23rd annual meeting of the Ocular Microbiology and Immunology Group was held Oct. 28, 1989, in New Orleans.

T. J. Liesegang reported an epidemiologic study of herpes simplex in residents from Rochester, Minnesota. Over a 33-year period, 122 residents had their first episode of ocular herpes simplex virus infection for an age and sex adjusted incidence rate of 8.4 new cases per 100,000 person-years. These initial episodes mostly involved the eyelid, conjunctiva, or superficial cornea. Age-adjusted rates by sex were comparable and there was no seasonal trend. Significant complications were uncommon, and 90% of eyes maintained visual acuity of 20/40 or better.

A. E. Schwartz, A. Sugar, R. F. Meyer, and V. M. Elner described five patients who developed scleral necrosis as a complication of ocular herpes simplex. All patients had severe and complicated courses, severe pain, and visual loss. All patients developed an area of "porcelain" white sclera and moderate to severe uveitis. Four patients required corneal transplants and one required a conjunctival flap. Eventually, four eyes required enucleation for control of pain. Prompt and aggressive treatment could possibly have been beneficial.

A. H. Wander, H. C. Bubel, K. Moser, and H. R. Bloom used collagen corneal shields in experimental herpetic keratitis. These shields had no significant effect on the natural course of herpes simplex in guinea pigs, whether or not they were soaked in trifluridine. Collagen shields soaked in an antiviral could be used instead of conventional eyedrop therapy. Changing the shield daily, however, may not be convenient for the patient.

S. C. Pflugfelder, C. A. Crouse, I. C. Pereira, and S. Atherton evaluated tissue from Sjögren's syndrome patients using polymerase chain reaction to look for Epstein-Barr virus DNA sequences. Epstein-Barr virus DNA sequences were detected in 50% of peripheral blood mononuclear cells, 80% of lacrimal glands, and 80% of tear specimens. Epstein-Barr virus may play a role in ocular surface changes, lymphocytic proliferations in lacrimal glands, and polyclonal B cell activation observed in Sjögren's syndrome.

R. P. Kowalski, M. O. Ritter, and Y. J. Gordon reported enzyme immunofiltration, a new method for typing ocular adenovirus. The new test is fast and easy to interpret and is useful for routine identification of adenovirus.

K. F. Tabbara, O. M. Al Omar, and S. Al Habib described two patients who suffered eyelid lacerations from desert foxes, which led to rabies. Despite treatment with rabies immunoglobulin and rabies vaccine, one patient died of cerebral infection with rabies. Rabies prophylaxis is essential in patients sustaining lacerations from the bites of stray canines.

D. A. Jabs, J. Wingard, W. R. Green, E. R. Farmer, G. Vogelsang, R. Saral, and G. W. Santos described conjunctival graft vs host disease, which occurred in 19 of 263 patients who had bone marrow transplants. The competent bone marrow cells attack the immunocompetent host in this condition. The patients who had conjunctival involvement had a 90% mortality and a mean survival of 76 days. Therefore, conjunctival involvement may be a marker for severe graft vs host disease.

L. S. Fujikawa studied sequential conjunctival biopsies from six patients with severe uveitis or scleritis treated with oral cyclosporine. She found a significant decrease in the expression of the tissue antigens HLA-DR and HLA-DQ, particularly on the vascular endothelium. The results indicate a potent ocular response to cyclosporine and suggest that histocompatibility antigen expression on the vascular endothelium may be one of the mechanisms by which cyclosporine exerts its immunosuppressive effect.

C. M. Kalsow studied the relationship between the retina and pineal gland in systemic sensitization with retinal antigens. Sensitized rats demonstrated Ia antigen expression of the

retinal vascular endothelium. There was also expression of glial fibrillary acidic protein in the Muller cells of the retina, but not in the pineal glands. The response of the pineal to autoantigen sensitization may modulate the response observed in the retina.

R. A. Copeland, S. Weissman, H. B. Ostler, R. Biswell, and T. Daniels described two patients with cicatrizing conjunctivitis and ulcerative periodontal disease developed ocular linear IgA disease. Conjunctival biopsies disclosed IgA and fibrinogen in a bright linear pattern in the basement-membrane zone. These patients responded to dapsone treatment. Linear IgA disease is uncommon but should be considered in patients with cicatrizing ocular disease.

G. O. D. Rosenwasser described a 54-year-old man with ectrodactyly, ectodermal dysplasia, and cleft palate who had bilateral keratitis, ankyloblepharon, sparse eyebrows, and fine sparse cilia. Meibomian glands were absent. This rare congenital abnormality may occur with a bilateral keratitis because of ocular surface changes related to tear and conjunctival surface abnormalities. The inheritance is autosomal dominant.

R. B. Greene and P. Lankston reported regional mapping of the conjunctiva by impression cytology. The microscopic image of each filter paper disk can be digitized on a computer to monitor diseases and the effects of therapy.

S. S. Weissman, C. Pavesio, D. N. Skorich, H. B. Ostler, R. Breitbach, C. R. Dawson, and T. E. Daniels reported the conjunctival manifestation of lichen planus. They noted bilateral lacy subepithelial conjunctival scarring, shortening of the fornix, and superior conjunctival ulceration. A characteristic direct immunofluorescence pattern showed linear fibrinogen deposition without immunoglobulin or complement in the basement-membrane zone or superficial substantia propria.

K. J. Johns and E. B. Feinberg described a 35-year-old man who developed sympathetic ophthalmia 30 years after a perforating injury. Despite treatment with systemic corticosteroids and cytotoxic agents, the patient lost vision completely.

M. A. Terry and J. J. Rowsey reviewed 130 cases of endophthalmitis. Forty-three percent of cases occurred after cataract extraction and 19% occurred after trauma. Diagnostic vitrectomy yielded a 75% recovery of organisms. Gram-positive cocci accounted for 52% of the organisms. Final vision was highly correlated with preoperative vision. The presence of a virulent organism was also an important prognostic factor.

B. C. Joondeph, H. W. Flynn, and D. Miller reported a new culture method for infectious endophthalmitis. Vitreous specimens obtained during vitrectomy were injected into blood culture bottles. This method was found to be superior to a membrane filter system and direct plating.

S. S. Huang, T. P. O'Brien, J. B. Dick, and R. G. Michels found that animal eyes that had undergone vitrectomy were less susceptible to intraocular infection with *Staphylococcus epidermidis*. They postulate that removal of the vitreous or alteration of the vitreous matrix may allow more efficient clearance of organisms and decrease the susceptibility to infection.

A. Mansour, J. Barber, H. Li, H. Lucia, M. Rajashakar, and T. Margo reported vitreous replacement by gas as a therapeutic modality in bacterial endophthalmitis. Rabbits had vitrectomy, and the vitreous was replaced with 20% perfluoropropane. The gas-filled eyes demonstrated less inflammation. Antibiotic levels were similar in eyes with or without gas. Thus, ocular levels of systemic antibiotics can be achieved when the vitreous is replaced by gas. Additionally, vitrectomy removes potential growth factors and permits better visualization of the fundus.

M. Mayers, D. Payne, A. Agocha-Madu, M. Motyl, and M. Miller developed an animal model to study the pharmacokinetics of antibiotic drug penetration into the anterior chamber. Repeated paracenteses did not affect the drug entry or pharmacokinetics. These studies permit objective analysis of antibiotic penetration.

D. Payne, A. Agocha-Madu, M. Mayers, M. Motyl, and M. Miller compared the anterior chamber pharmacokinetics of amikacin and chloramphenicol after intravenous and direct injection of the drug. Their data suggest that for selected compounds that traverse the blood-ocular barrier, the intravenous route may be theoretically advantageous.

J. Baum and G. Zaidman discussed the protean clinical manifestations of Lyme disease keratitis. They described three patients who developed bilateral keratitis long after the systemic disease was diagnosed and treated. Corneal stroma infiltrates differ greatly in their occurrence and are not associated with significant corneal damage. The keratitis is amenable to treatment with topical corticosteroids and may have an immunologic pathogenesis.

S. E. Orlin also discussed a case of Lyme keratitis in a 19-year-old woman who had been treated two years earlier for the disease. The keratitis appeared as multiple small infiltrates at all levels of the stroma and responded well to topical corticosteroid therapy. The author also believed that the keratitis was a hypersensitivity response to *Borrelia burgdorferi*.

J. Colin, F. Malet, and A. M. Simitzis discussed the epidemiology of *Acanthamoeba* keratitis in France. Only six cases have been identified; the low incidence may reflect the absence of homemade saline solution in France.

M. Osoto, M. Pyron, M. Elanzo, and K. R. Wilhelmus discussed the pathogenesis of amebic keratitis. They isolated human corneal epithelial sheets in tissue culture and examined the adherence and penetration capabilities of the cysts and trophozoites of *Acanthamoeba*. Both forms of ameba adhered well to the corneal cells and penetrated the cells within three hours of inoculation.

C. M. Kirkness, A. K. Bates, and L. A. Ficker reported 30 cases of microbial keratitis after penetrating keratoplasty. This represents 3% of corneal transplants performed during a five-year period. Risk factors for infection include dry eye, conjunctival scarring, loose sutures, excessive topical corticosteroids, contact lenses, and ocular surface disease.

M. L. Gilbert, J. D. Gottsch, M. Sulewski, and W. J. Stark used the excimer laser to treat microbial keratitis in the rabbit. The laser treatment reduced but did not eliminate mycobacteria and *Fusarium*. The excimer laser may have a role in treating anterior focal infections rather than advanced corneal infections.

J. J. Reidy, J. A. Hobden, R. J. O'Callaghan, and J. M. Hill treated experimental *Pseudomonas* keratitis with collagen shields containing tobramycin and dexamethasone. Supplemental eyedrops were given every two hours for either eight or 24 hours. In this system, treatment with tobramycin was superior to tobramycin plus dexamethasone in sterilizing corneas. The results suggest that the use of topical corticosteroids in bacterial keratitis be delayed for at least 24 hours after beginning antibiotic therapy.

T. P. O'Brien, K. R. Wilhelmus, and M. S. Osoto examined the effect of topical quinoline therapy on experimental *Streptococcus pneumoniae* keratitis. Treatment with tosufloxacin and penicillin resulted in a significant reduction of organisms compared to eyes treated with ciprofloxin, norfloxacin, or normal saline. Streptococci are considered to be resistant to most quinoline antibiotics.

W. B. Neusidel and J. W. Cowden described a patient with a severe *Pseudomonas* corneal ulcer that extended into the adjacent sclera leading to a nodular scleral abscess separate from an area of sclerokeratitis. The patient then developed proptosis, choroidal effusion, and a retinal detachment. Despite treatment, unbearable pain led to enucleation. Histology demonstrated intrascleral abscesses. This report supports the concept that *Pseudomonas* corneal infections that extend into the sclera do not respond to medical therapy.

M. R. Sawusch and P. J. McDonnell reported two cases of microbial keratitis associated with disposable soft contact lenses. One patient changed her lenses every two weeks and developed *Pseudomonas* keratitis after a four-day period of wear. The second patient changed her lenses every week and developed bacterial keratitis after a one-day period of wear. The same degree of care, patient selection, instruction, and follow-up must be used for disposable lenses as for conventional, extended-wear, or daily-wear lenses.

H. Kattan, S. C. Pflugfelder, D. Miller, and D. C. Tse reported a case of *Nocardia* scleritis in a patient who had a scleral buckle 15 years earlier. She had a cataract extraction three years before the infection and wore soft contact lenses daily. Despite treatment with Bactrim and other antibiotics, the eye had to be enucleated.

M. Nanda and S. C. Pflugfelder reported three cases of *Pseudomonas* keratitis in patients with human immunodeficiency virus infection. Two of the patients wore extended-wear soft contact lenses and the authors recommend that HIV-positive patients not wear extended-wear contact lenses.

S. M. Stenson, D. Friedberg, and P. Tierno reported bilateral superficial keratitis in three patients with acquired immunodeficiency virus, one of whom was culture positive for the protozoa microsporidia. The organism has been identified in other tissues of AIDS patients and should be suspected in any case of recalcitrant keratitis with negative cultures in AIDS patients.

R. A. Eiferman, K. T. Flaherty, and A. K. Rivard reported a persistent corneal defect caused by *Listeria monocytogenes*. The patient had a history of alcohol abuse and an irritated right eye for five days. The cornea healed uneventfully with topical gentamicin and a temporary tarsorrhaphy.

C. M. Parrish, W. S. Head, T. E. Williams, and D. M. O'Day described a 71-year-old patient who developed a large corneal ulcer while wearing a bandage contact lens for bullous keratopathy. Corneal biopsy showed *Aspergillus* species. Subsequent penetrating keratoplasty led to a culture of *Bacillus cereus* from the cornea and a fibrous membrane. This isolate was possibly a low toxin producer and was less pathogenic than other strains of the organism.

D. M. O'Day, K. A. Klippenstein, R. D. Robinson, T. E. Williams, and W. S. Head described a rapid in vivo method for screening antifungal agents for subconjunctival injection in the treatment of keratomycosis. The agent to be tested is injected at the superior limbus of rabbit eyes, and the corneas are placed on agar plates containing an indicator organism. After incubation for 24 hours, the plates are read for zones of inhibition.

T. John and E. Lehman reported a case of unilateral corneal ulceration caused by *Corynebacterium* Johnson-Kaye superimposed on an infection of *Candida albicans*. Vancomycin and antifungal agents were used, and a penetrating keratoplasty was also necessary.

S. T. Berger, D. Katsev, T. H. Pettit, and B. J. Mondino reported a case of *Curvularia* species keratitis related to a metallic foreign body injury. The lesion appeared as a gray-white, elevated plaque with brown pigmentation in a branching pattern within the anterior stroma. This pigmentation may be a helpful clue in the early diagnosis of dematiaceous fungal keratitis.

H. D. Perry and E. D. Donnenfeld described a patient who developed a *Cryptococcus neoformans* keratitis after penetrating keratoplasty. The patient responded to therapy with topical miconazole.

I. Brunette and R. D. Stulting described a patient who developed scleritis because of a *Sporothrix schenckii* infection after injury to the eye with a flying chip of wood. Miconazole and amphotericin B treatment contributed to the healing of the necrotic scleral ulcer.

A. Y. Matoba, T. P. O'Brien, N. M. Robinson, and M. S. Osoto reported the addition of vancomycin to gentamicin to enhance the antimicrobial activity of McCarey-Kaufman medium. Vancomycin is much more active against streptococci than gentamicin is.

A. T. Folkens, G. A. Cupp, D. A. Schlech, and R. L. Abschire reported a study in which ciprofloxacin ophthalmic solution was used to treat chronic blepharitis and blepharoconjunctivitis. The antibiotic was remarkably effective in eradicating or significantly reducing the numbers of organisms. The antimicrobial effect was evident five days after therapy had been completed. The drug appears to be equivalent to tobramycin in its antimicrobial activity.

L. A. Ficker, D. Seal, and P. Wright discussed the role of staphylococcal toxin in blepharitis. They identified a novel toxin but believed that toxin production did not have a strong pathogenic role in blepharitis.

Y.-K. Au, M. D. Reynolds, and E. D. Rambin described a patient with a purulent conjunctivitis in whom *Neisseria cinerea* was cultured. Clinical features were similar to gonococcal infections. The patient responded to treatment with intravenous ceftriaxone and topical erythromycin.

M. Volpicelli, J. C. Barber, and T. L. Schwartz reported the management of acute suppurative dacryocystitis. Causes included sinusitis, trauma, involutional changes, and tumor. *Staphylococcus epidermidis*, alpha hemolytic streptococcus, and gram-negative rods were the most common isolates. Half of the patients required parenteral therapy after failure of oral antibiotics.

J. B. Robin, R. Chan, and J. Johanson compared the sensitivity of fluorescein-conjugated lectins to provide rapid visualization of several classes of microorganisms. F-ConA appeared to be as sensitive as Gram staining for bacteria. F-ConA was significantly better, however, for visualization of fungi and *Acanthamoeba*.

G. N. Kervick, E. L. Fonso, and D. Miller discussed the antibiotic sensitivity of *Bacillus* species. The authors recommend combination treatment with gentamicin and vancomycin or ciprofloxacin and imipenem. Some resistance to clindamycin does exist.

J. H. Brinser compared anaerobic media for ocular microbiology. He recommended prereduced anaerobically sterilized media as the medium of choice with chocolate agar being the second choice.

J. D. Lanier and R. H. Bullington reported several cases of microbial keratitis caused by five species of mycobacteria. These infections occur in immunocompromised patients, including those with AIDS.

MITCHELL H. FRIEDLAENDER

ABSTRACT DEPARTMENT

Edited by David Shoch, M.D.

American Journal of Cardiology

Superior antiplatelet action of alternate day pulsed dosing versus split dose administration of aspirin. Lorenz, R. L., Boehlig, B., Uedelhoven, W. M., and Weber, P. C. (Medizinische Klinik Innenstadt der Universitat, Ziemssenstrasse 1, 8000 Munich 2, West Germany). Am. J. Cardiol. 64:1185, 1989.

To differentiate the desirable inhibition of platelet aggregation and thromboxane formation by aspirin from an unwanted simultaneous suppression of prostacyclin, low doses and slow release preparations of aspirin have been suggested. In the present study, a mean amount of 40 mg of aspirin each day was administered in 20-mg doses twice daily, a single 40-mg dose daily, or a single 80-mg dose every other day and compared to a dose of 324 mg daily. Bleeding time, serum thromboxane, collagen-stimulated platelet aggregation (and associated thromboxane formation), and excretion of thromboxane and prostacyclin metabolites were measured at the peak and trough of drug action. The inhibiting effects on platelet aggregation and associated thromboxane formation were least marked with 20 mg twice daily, intermediate with 40 mg daily, and best with 80 mg every other day. All were less than that with a 324-mg dose daily. All regimens suppressed thromboxane formation more than 80%. Prostacyclin metabolite excretion was similar for all 40-mg/day regimens but more pronounced after 324 mg/day. (3 figures, 26 references)

American Journal of Clinical Nutrition

Nutritional factors in diabetics with and without retinopathy. Roy, M. S., Stables, G., Collier, B., Roy, A., and Bou, E. (Natl. Eye Inst., Bldg. 10, Room 10C410, Bethesda, MD 20892). Am. J. Clin. Nutr. 50:728, 1989.

Thirty-four diabetic patients were divided into two groups, 15 patients with retinopathy and 19 patients without. The patients were asked to record their food intake for three days so that nutritional factors could be evaluated. The patients without retinopathy had significantly higher daily intakes of total carbohydrates, fiber, and glucose than did patients with retinopathy. Additionally, the patients without retinopathy had a lower protein intake than those with retinopathy. There is now evidence that high carbohydrate/high fiber diets improve diabetic control and lower insulin requirements and serum lipids. The choice of particular foods, however, may be more important than the absolute fiber content of the diet. (2 figures, 23 references)—David Shoch

Conjunctival impression cytology for assessment of vitamin A status. Reddy, V., Rao, V., Reddy, A., and Reddy, M. (Natl. Inst. Nutr., Jamai-Osmania, Hyderbad-500007, India). Am. J. Clin. Nutr. 50:814, 1989.

Ocular signs and serum vitamin A concentrations are commonly used for the diagnosis of vitamin A deficiency. Recently, impression cytology was suggested to detect this condition. A clinical trial was conducted to compare the results of impression cytology with two other indicators of vitamin A status. A total of 246 children aged 1–10 years were studied. Abnormal cytology was present in about 25% of the children with normal eyes. Their mean vitamin A concentrations were significantly lower compared with those with normal cytology, which suggests that the abnormal cytology reflected subclinical deficiency. After treatment with vitamin A, most of the children who had abnormal cytology at baseline examination showed improvement. These observations suggest that abnormal conjunctival cytology is specific to vitamin A deficiency. Impression cytology is a relatively simple technique and can be used for assessing the magnitude of the problem, especially in communities where the prevalence of clinical disease is low. (5 tables, 14 references)—Authors' abstract

Archives of Internal Medicine

Prospective study of *Candida* endophthalmitis in hospitalized patients with candidemia. Brooks, R. G. (Dept. Intern. Med., Orlando Regional Med. Ctr., 1414 S. Kuhl Ave., Orlando, FL 32806). Arch. Intern. Med. 149:2226, 1989.

To determine the frequency of endogenous *Candida* endophthalmitis in patients with candidemia, we prospectively evaluated 32 inpatients with fungemia by weekly indirect ophthalmoscopic examinations. Chorioretinitis compatible with *Candida* infection was found in 9 (28%) patients. Patient age, sex, underlying diseases, or hospital-acquired factors, such as presence of central venous or Foley catheters, bacteremia, use of multiple antibiotics, hyperalimentation, or surgery, did not distinguish between groups. Groups were also similar in number of sites colonized with yeast and species of *Candida* recovered. Patients with endophthalmitis tended to have more blood cultures positive for *Candida* (mean, 4.3) than the patients without endophthalmitis (mean, 2.8), but this trend did not reach statistical significance. Based on these results, we recommend periodic ophthalmoscopic examinations in all patients with documented candidemia. (1 table, 11 references)—Author's abstract

Clinical Toxicology

Cyanoacrylates and corneal abrasion. Dean, B. S., and Krenzelok, E. P. (Pittsburgh Poison Ctr., Children's Hosp. of Pittsburgh, Pittsburgh, PA 15213). Clin. Toxicol. 27:169, 1989.

The authors studied 34 incidents of ocular adhesions by cyanoacrylate-containing solutions. Twenty-one episodes occurred in adults and 13 occurred in children. In each case the contaminated eyes were thoroughly irrigated with warm water for 15 minutes. Mineral oil was applied to the external surface in two patients. Fifteen of the patients suffered corneal abrasions, which necessitated treatment with antibiotics, cycloplegics, and patching. Often, the patients with corneal abrasions had delayed the decontamination for 15 minutes or more. There were no cases of permanent corneal damage.

The authors recommend immediate irrigation of the eyes and continued irrigation with warm water for at least 15 minutes. If mineral oil is available, it may help break the adhesive effect of the cyanoacrylates. The authors advise external application of mineral oil to eyelid surfaces after the irrigation. If there is a delay for more than 15 minutes in treatment, a thorough ophthalmic examination is advised. (6 references) —David Shoch

Graefe's Archive for Clinical and Experimental Ophthalmology

Vasoconstrictive effect of topical timolol on human retinal arteries. Martin, X. D., and Rabineau, P. A. (Universitats-Augenklinik Raemistrasse 100, CH-8091, Zurich, Switzerland). Graefes Arch. Clin. Exp. Ophthalmol 227:526, 1989.

The exact mechanism by which beta blockers reduce intraocular pressure has not been determined. The authors suggest that beta blockers may constrict ciliary arteries, thereby lowering intraocular pressure. To determine whether or not such vasoconstriction occurs, the authors examined 12 patients with normal eyes after the instillation of 0.5% timolol twice daily in one eye for one week. Nine of the patients had a diminution of arterial size in the treated eye. The mean decrease was 4.1% in treated eyes ($P < .05$). No statistical difference was found in veins. Because timolol seems to have a vasoconstrictive effect on the retinal arterioles of normal human subjects, it is possible that this effect also occurs in the ciliary arteries, which might result in the lowering of intraocular pressure. (3 figures, 3 tables, 47 references)—David Shoch

Electroretinography in central retinal vein occlusion. Correlation of electroretinographic changes with pupillary abnormalities. Hayreh S. S., Klugman, M. R., Podhajsky, P., and Kolder, H. E. (Dept. Ophthalmol. and Dept Preven. Med., Univ. Iowa, Iowa City, IA 52242) Graefes Arch. Clin. Exp. Ophthalmol. 227:549 1989.

In 149 eyes with central retinal vein occlusion, we prospectively investigated the role of routine, clinical electroretinography in differentiating ischemic (60 eyes) from nonischemic central vein occlusion (89 eyes). Single-flash photopic and scotopic electroretinograms were recorded. Data for the amplitudes and implicit times of a- and b-waves and for the b-/a-wave amplitude ratio were analyzed in detail. The study revealed that the best electroretinography parameter (for both photopic and scotopic electroretinography) was a subnormal b-wave amplitude (reduced to $\leq 60\%$ or by ≥ 1 standard deviation from the normal mean value, or $\leq 64\%$–69% of that in the fellow normal eye), with a sensitivity of 80%–90% and a specificity of 70%–80%. Electroretinography

findings were correlated with the relative afferent pupillary defect. A relative afferent pupillary defect of ≥ 0.7 log units showed a sensitivity of 88% and a specificity of 90% in differentiating ischemic from nonischemic central retinal vein occlusion. Electroretinography and relative afferent pupillary defect findings showed a good correlation. The combined electroretinography and relative afferent pupillary defect tests could differentiate 97%–100% of ischemic from nonischemic central retinal vein occlusion cases, with a specificity of about 70%. (1 figure, 6 tables, 29 references)—Authors' abstract

Investigative Ophthalmology & Visual Science

Diabetic-like retinopathy in rats prevented with an aldose reductase inhibitor. Robison, W. G., Nagata, M., Laver, N., Hohman, T. C., and Kinoshita, J. H. (Bldg. 9, Room 1E-104, Natl. Eye Inst., Natl. Inst. Health, 9000 Rockville Pike, Bethesda, MD 20892). Invest. Ophthalmol. Vis. Sci. 30:2285, 1989.

The earliest histopathologic signs of diabetic retinopathy include selective loss of intramural pericytes and thickening of capillary basement membranes. Previous evidence from animal models indicated that aldose reductase inhibitors could prevent these capillary wall lesions, but only recently have aldose reductase inhibitors been tested for prevention of the subsequent retinal complications of diabetes, such as microaneurysms. In the present study, Sprague-Dawley rats were fed diets containing 50% galactose with or without an aldose reductase inhibitor (tolrestat). After 28 months of galactose feeding, the retinal capillaries in whole mounts exhibited a marked increase in periodic acid-Schiff (PAS) staining, extensive pericyte loss, endothelial cell proliferation, acellularity, diffuse dilation, occluded lumens, microaneurysms, and complex microvascular abnormalities including gross dilation and formation of multiple shunt networks. The PAS hyperchromaticity of basement membrane material and pericyte loss occurred throughout the retinal vasculature, while the microaneurysms and complex lesions were limited to the capillaries of the central and paracentral retina. The changes were associated with both the arterial and venous portions of the capillary plexus. Treatment with orally administered tolrestat prevented essentially all of the vessel abnormalities. Thus, long-term galactose feeding of rats induced microvascular lesions simulating those occurring in background diabetic retinopathy in humans, and these lesions were prevented by treatment with an aldose reductase inhibitor. (3 figures, 30 references)—Authors' abstract

Journal of Medical Genetics

Cat eye syndrome associated with aganglionosis of the small and large intestine. Ward, J., Sierra, I. A., and D'Croz, E. (P.O. Box 10-378, Zona 4 Panama, Panama). J. Med. Genet. 26:647, 1989.

The cat-eye syndrome is characterized by anal atresia, ocular coloboma, cardiac defects, preauricular tags or sinuses, abnormalities of the urinary tract, mental retardation, and a supernumerary, bisatellited, isodicentric chromosome. The isodicentric chromosome carries three or four copies of D22S9 mapping at 22q11. A newborn boy born after 38 weeks' gestation had a coloboma of the iris, anal atresia, preauricular pits, and bilateral cryptorchidism. Cytogenetic studies of peripheral blood cells showed 47 chromosomes in all cells, with a supernumerary chromosome smaller than a G chromosome. The karyotype of both parents was normal. The unusual feature in this patient was the absence of parasympathetic ganglion cells throughout the intestinal tract. This association, however, may be coincidental. (2 figures, 2 references)

New England Journal of Medicine

Myocardial infarction after ophthalmic betaxolol (letter). Chamberlain, T. J. (Montrose Mem. Hosp., Montrose, CO 81401). N. Engl. J. Med. 321:1342, 1989.

An 81-year-old man had well-controlled hypertension for which he was taking atenolol (25 mg per day) and indapamide (2.5 mg per day). He placed a single drop of 0.5% ophthalmic betaxolol hydrochloride into his left eye, and within 5 minutes felt faint and collapsed. He was unconscious for less than a minute and on awakening he felt jaw pain which progressed to crushing anterior chest pain. An electrocardiogram showed the classic changes of an acute

inferior myocardial infarction. The pathophysiologic mechanism that resulted in the myocardial infarction may have been coronary vasospasm mediated by alpha-adrenergic receptors, although severe hypotension or bradyarrhythmia cannot be excluded. The patient may have been predisposed to this side effect as a consequence of his concurrent use of oral atenolol. There is a potential for systemic toxicity after topical beta blockade and beta blockers must be administered cautiously to elderly patients who have glaucoma. (6 references)

Plastic and Reconstructive Surgery

Surgical treatment of thyrotoxic exophthalmos. Roncevic, R., and Jackson, I. T. (Inst. Craniofacial, Plast. & Reconstr. Surg., Providence Hosp., 16001 1 W. Nine Mile Rd., P.O. Box 2043, Southfield, MI 48037). Plast. Reconstr. Surg. 84:754, 1989.

Decompression of the orbit was performed in 17 patients with 24 to 32 mm of thyrotoxic exophthalmos. Fifteen patients were women, aged 28 to 65 years, and two were men, aged 28 and 51 years. At the beginning of the procedure, a blepharorrhaphy was made using two or three single sutures. These were removed five to seven days after the operation. The initial step was removal of fat within the upper eyelid and division of the aponeurosis of the levator palpebrae muscle. An incision was made in the lower eyelid 3 mm below its margin through which the floor and lateral wall of the orbit were exposed. As much periorbital fat as possible was removed. The posterior portion of the orbital floor and the zygomatic portion of the lateral orbit wall were excised with a small chisel and hemostat. The bony bridge between the floor and the lateral wall defect were removed to create a large orbitectomy. Through a medial incision, the medial orbital wall was explored and the ethmoidal section of the wall was removed. This defect was made continuous with the defect in the orbital floor. (5 figures, 13 references)

The Proceedings of the Institute of Medicine of Chicago

The control of intraocular pressure by dopamine 1 (DA_1) receptors. Karnezis, T. (University of Chicago). Proc. Inst. Med. Chgo. 42:69, 1989.

Absence of specific agonists and antagonists until recently has precluded investigation of the role of dopamine receptors in the control of intraocular pressure. Intravenous infusion of fenoldopam, a novel selective dopamine receptor agonist, increased intraocular pressure in 8 healthy volunteers from 14.6 ± 0.9 to 17.6 ± 1.4 mm Hg ($P < 0.05$). In a study of patients with severe systemic hypertension, fenoldopam elevated intraocular pressure in a dose-related fashion by 26% while lowering blood pressure. There was no effect on pupil diameter.

The effects of dopamine and fenoldopam on cAMP metabolism in trabecular meshwork was investigated. Incubation of trabecular meshwork with fenoldopam produced a 4 fold increase in cAMP content from 24.4 ± 1.9 to 101.8 ± 6.3 pmol/mg protein. Although less potent, dopamine paralleled this response. Preincubation with a $dopamine_1$ receptor antagonist, but not with alpha or beta receptor antagonists, phenoxybenzamine or propranolol respectively, inhibits this increase by 90%.

These results demonstrate that dopamine receptor activation increases intraocular pressure in man independent of changes in systemic blood pressure, and suggest that this effect may be mediated by stimulation of adenylate cyclase-linked $dopamine_1$ receptors in the trabecular meshwork of eyes. This finding may provide a new approach for pharmacologic regulation of intraocular pressure in patients with glaucoma. (9 figures, 36 references) -Author's abstract

Correction

The title of the article by Riri S. Manor, published in November (Am. J. Ophthalmol. 108:585, 1989), was incorrect as submitted by the author. The correct title is as follows: "Entoptic phenomena in pregeniculate and postgeniculate hemianopsia with splitting of macula by perimetry."

NEWS ITEMS

Send News Items to
American Journal of Ophthalmology
435 N. Michigan Ave., Suite 1415
Chicago, IL 60611

The Journal invites readers to submit announcements concerning meetings, postgraduate courses, lectures, honors, and appointments. Each item must be typed double-spaced on bond paper with 1½-inch margins. Only one news item should be submitted on each page. Announcements concerning meetings and courses must contain the title, location, dates, sponsors, and address required for additional information. Each item must not exceed 75 words in length and be prepared in narrative, not outline, form. Announcements of meetings and courses must be received at least four months before the event.

Nadi Al Bassar North African Center for Sight: Pediatric Ophthalmology Course

The Nadi Al Bassar North African Center for Sight: Pediatric Ophthalmology Course will be held Sept. 10–15, 1990, in Tunis, Tunisia. For further information, write Nadi Al Bassar, 9 Blvd. Bab Menara, 1008 Tunis, Tunisia.

Fifth Annual National Eye Trauma Symposium

The Fifth Annual National Eye Trauma Symposium, sponsored by the University of Texas Southwestern Medical Center at Dallas and the National Eye Trauma System, and cosponsored by Alcon Laboratories, Inc., will be held April 19–21, 1990, at the Westin Hotel Galleria, Dallas. For further information, write Eleanor Goldsmith, Department of Ophthalmology, University of Texas, Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas TX 75235; telephone (214) 688-3848.

Allegheny Ophthalmic & Orbital Center and Allegheny General Hospital Department of Neurosurgery: Advanced Orbital Surgery Course

The Allegheny Ophthalmic & Orbital Center and Allegheny General Hospital Department of Neurosurgery: Advanced Orbital Surgery Course, Techniques and Practical Experience, will be held April 20 and 21, 1990. For further information, write Continuing Medical Education, Allegheny General Hospital, 320 E. North Ave., Pittsburgh, PA 15212.

Chicago Ophthalmological Society: 42nd Annual Clinical Conference

The Chicago Ophthalmological Society: 42nd Annual Clinical Conference will be held May 24 and 25, 1990, at the Hotel Inter-Continental, Chicago. For further information, write Julie Hughes, Chicago Ophthalmological Society, 515 N. Dearborn, Chicago, IL 60610; telephone (312) 670-2583.

Cornell Medical Center: Diagnostic Imaging of the Eye and Orbit: Ultrasound, CT and MRI Course

The Cornell Medical Center: Diagnostic Imaging of the Eye and Orbit: Ultrasound, CT and MRI Course will be held June 1 and 2, 1990, in New York City. For further information, write Suzanne Woods, Department of Ophthalmology, Cornell University Medical College, 520 E. 70th St., New York, NY 10021; telephone (212) 746-2504.

Corneal Associates of New Jersey: Second Annual Corneal Symposium

The Corneal Associates of New Jersey: Second Annual Corneal Symposium, External Ocular Diseases and Refractive Surgery for the General Ophthalmologist, will be held April 21, 1990, in West Orange, New Jersey. For further information, write Barbara Mysko, Conference Coordinator, 101 Old Short Hills Rd., Suite 520, West Orange, NJ 07052; telephone (201) 736-1313.

The Dana Center for Preventive Ophthalmology: Third Mohammed Aziz Memorial Annual Lecture

The Dana Center for Preventive Ophthalmology: Third Mohammed Aziz Memorial Annual Lecture will be given on March 30, 1990, by Fred C. Hollows. The lecture will take place at the Wilmer Institute, Baltimore. The title of Professor Hollows's lecture is The Prevention of Blindness in the Tropics.

Florida Society of Ophthalmology: Annual Meeting and Scientific Session

The Florida Society of Ophthalmology: Annual Meeting and Scientific Session will be held

April 6–8, 1990, at the Marriott at Sawgrass Resort, Ponte Vedra Beach, Florida. For further information, write Florida Society of Ophthalmology, 1133 W. Morse Blvd., Suite 201, Winter Park, FL 32789; telephone (407) 647-8839.

Harvard Medical School: Innovations and Controversies in Cataract Surgery: Phacoemulsification, Small Incision and Multifocal IOLs, and Special Techniques Lectures and Wet Lab

The Harvard Medical School: Innovations and Controversies in Cataract Surgery: Phacoemulsification, Small Incision and Multifocal IOLs, and Special Techniques Lectures and Wet Lab will be held June 2 and 3, 1990. For further information, write Ophthalmic Education, Massachusetts Eye and Ear Infirmary, 243 Charles St., Boston, MA 02114; telephone (617) 573-3526.

Jules Stein Eye Institute: Annual Postgraduate Seminar and 21st Jules Stein Lecture

The Jules Stein Eye Institute: Annual Postgraduate Seminar and 21st Jules Stein Lecture will be held April 6 and 7, 1990, at the Century Plaza Hotel, Los Angeles. For further information, write Gretchen Falvo, Director of Academic Programs, Jules Stein Eye Institute, 100 Stein Plaza, UCLA, Los Angeles, CA 90024; telephone (213) 825-4617.

Manhattan Eye, Ear, and Throat Hospital: Fluorescein Workshop

The Manhattan Eye, Ear, and Throat Hospital: Fluorescein Workshop will be held March 24, 1990, in New York. For further information, write Francine Leinhardt, Course Coordinator, Manhattan Eye, Ear, and Throat Hospital, 210 E. 64th St., New York, NY 10021; telephone (212) 838-9200, ext. 2776.

St. Mary's Hospital and Medical Center, San Francisco: Retina Workshops

The St. Mary's Hospital and Medical Center, San Francisco: Retina Workshops will be held May 4 and 5 and May 11 and 12, 1990. For further information, write Lorraine Geary, c/o Howard Schatz, M.D., 1 Daniel Burnham Court, 210C, San Francisco, CA 94109; telephone (415) 441-0906.

University of Illinois at Chicago: Eighth Annual Clinical Challenges Day

The University of Illinois at Chicago: Eighth Annual Clinical Challenges Day will be held March 14, 1990, at the University of Illinois Hospital Eye and Ear Infirmary. For further information, write Catherine M. Brod, Program Director, University of Illinois at Chicago, Eye and Ear Infirmary, 1855 W. Taylor St., Chicago, IL 60612; telephone (312) 996-4747.

University of Minnesota: Ocular Trauma, Lasers, and Fluorescein Angiography Course

The University of Minnesota: Ocular Trauma, Lasers, and Fluorescein Angiography Course will be held April 2 and 3, 1990, at the Radisson University Hotel, Minneapolis. For further information, write Becky Noren, Registrar, University of Minnesota, Continuing Medical Education, Box 202 UMHC, 420 Delaware St. S.E., Minneapolis, MN 55455; telephone (612) 626-5525.

University of Missouri—Kansas City School of Medicine: Excimer Laser Course

The University of Missouri--Kansas City School of Medicine: Excimer Laser Course both refractive and therapeutic, will be held June 15 and 16, 1990, at the Eye Foundation of Kansas City. For further information, write John W. Irvine, Eye Foundation of Kansas City, 2300 Holmes, Kansas City, MO [illegible]; telephone (816) 881-6150.

University of Pittsburgh: Pediatric Ophthalmology for the Ophthalmologist and Pediatrician Update

The University of Pittsburgh: Pediatric Ophthalmology for the Ophthalmologist and Pediatrician Update will be held March 17, 1990, at McClusky Auditorium, Children's Hospital of Pittsburgh. For further information telephone Ms. Barbara Butt at (412) 6[illegible]-2256 or Ms. Maria Moore at (41[illegible]) 682-630[illegible].

University of Tennessee: 19th Annual Alumni-Residents Day and Memphis Eye Convention

The U[illegible]

Memphis. For further information telephone (901) 528-5883.

Virginia Society of Ophthalmology: Annual Meeting

The Virginia Society of Ophthalmology: Annual Meeting will be held June 22–24, 1990, at the Omni International Hotel, Norfolk. For further information, write Donna Scott, 4205 Dover Rd., Richmond, VA 23221; telephone (804) 353-2721.

American Society of Ophthalmic Plastic and Reconstructive Surgery: New Officers

American Society of Ophthalmic Plastic and Reconstructive Surgery: New Officers are as follows: Bernice Z. Brown, president; Arthur S. Grove, president-elect; John A. Burns, vice-president; Daniel L. McLachlan, executive secretary; George L. Paris, treasurer; William R. Nunery, secretary; Paul T. Gavaris, program chairman; Bradley Lemke, assistant program chairman; and Clinton D. McCord, Jr., immediate past president and chairman of the advisory committee.

Research to Prevent Blindness: Senior Scientific Investigators

Research to Prevent Blindness announced four Senior Scientific Investigators. They are Robert E. Anderson, Department of Ophthalmology, Baylor College of Medicine; Robert L. Church, Department of Ophthalmology, Emory University; Peter Gouras, Department of Ophthalmology, Columbia University; and Wayne L. Hubbell, Department of Ophthalmology, University of California, Los Angeles.

Personal

Nicholas T. Iliff

Nicholas T. Iliff has been named full-time director of the oculoplastics service at the Wilmer Eye Institute, Baltimore.

April 6–8, 1990, at the Marriott at Sawgrass Resort, Ponte Vedra Beach, Florida. For further information, write Florida Society of Ophthalmology, 1133 W. Morse Blvd., Suite 201, Winter Park, FL 32789; telephone (407) 647-8839.

Harvard Medical School: Innovations and Controversies in Cataract Surgery: Phacoemulsification, Small Incision and Multifocal IOLs, and Special Techniques Lectures and Wet Lab

The Harvard Medical School: Innovations and Controversies in Cataract Surgery: Phacoemulsification, Small Incision and Multifocal IOLs, and Special Techniques Lectures and Wet Lab will be held June 2 and 3, 1990. For further information, write Ophthalmic Education, Massachusetts Eye and Ear Infirmary, 243 Charles St., Boston, MA 02114; telephone (617) 573-3526.

Jules Stein Eye Institute: Annual Postgraduate Seminar and 21st Jules Stein Lecture

The Jules Stein Eye Institute: Annual Postgraduate Seminar and 21st Jules Stein Lecture will be held April 6 and 7, 1990, at the Century Plaza Hotel, Los Angeles. For further information, write Gretchen Falvo, Director of Academic Programs, Jules Stein Eye Institute, 100 Stein Plaza, UCLA, Los Angeles, CA 90024; telephone (213) 825-4617.

Manhattan Eye, Ear, and Throat Hospital: Fluorescein Workshop

The Manhattan Eye, Ear, and Throat Hospital: Fluorescein Workshop will be held March 24, 1990, in New York. For further information, write Francine Leinhardt, Course Coordinator, Manhattan Eye, Ear, and Throat Hospital, 210 E. 64th St., New York, NY 10021; telephone (212) 838-9200, ext. 2776.

St. Mary's Hospital and Medical Center, San Francisco: Retina Workshops

The St. Mary's Hospital and Medical Center, San Francisco: Retina Workshops will be held May 4 and 5 and May 11 and 12, 1990. For further information, write Lorraine Geary, c/o Howard Schatz, M.D., 1 Daniel Burnham Court, 210C, San Francisco, CA 94109; telephone (415) 441-0906.

University of Illinois at Chicago: Eighth Annual Clinical Challenges Day

The University of Illinois at Chicago: Eighth Annual Clinical Challenges Day will be held March 14, 1990, at the University of Illinois Hospital Eye and Ear Infirmary. For further information, write Catherine M. Brod, Program Director, University of Illinois at Chicago, Eye and Ear Infirmary, 1855 W. Taylor St., Chicago, IL 60612; telephone (312) 996-4747.

University of Minnesota: Ocular Trauma, Lasers, and Fluorescein Angiography Course

The University of Minnesota: Ocular Trauma, Lasers, and Fluorescein Angiography Course will be held April 2 and 3, 1990, at the Radisson University Hotel, Minneapolis. For further information, write Becky Noren, Registrar, University of Minnesota, Continuing Medical Education, Box 202 UMHC, 420 Delaware St. S.E., Minneapolis, MN 55455; telephone (612) 626-5525.

University of Missouri—Kansas City School of Medicine: Excimer Laser Course

The University of Missouri—Kansas City School of Medicine: Excimer Laser Course, both refractive and therapeutic, will be held June 15 and 16, 1990, at the Eye Foundation of Kansas City. For further information write John W. Irvine, Eye Foundation of Kansas City, 2300 Holmes, Kansas City, MO 64108; telephone (816) 881-6150.

University of Pittsburgh: Pediatric Ophthalmology for the Ophthalmologist and Pediatrician Update

The University of Pittsburgh: Pediatric Ophthalmology for the Ophthalmologist and Pediatrician Update will be held March 17, 1990, at McClusky Auditorium, Children's Hospital of Pittsburgh. For further information telephone Ms. Barbara Butti at (412) 647-2256 or Ms. Maria Moore at (412) 682-6300.

University of Tennessee: 19th Annual Alumni-Residents Day and Memphis Eye Convention

The University of Tennessee: 19th Annual Alumni-Residents Day and Memphis Eye Convention will be held March 9–11, 1990, in

Memphis. For further information telephone (901) 528-5883.

Virginia Society of Ophthalmology: Annual Meeting

The Virginia Society of Ophthalmology: Annual Meeting will be held June 22–24, 1990, at the Omni International Hotel, Norfolk. For further information, write Donna Scott, 4205 Dover Rd., Richmond, VA 23221; telephone (804) 353-2721.

American Society of Ophthalmic Plastic and Reconstructive Surgery: New Officers

American Society of Ophthalmic Plastic and Reconstructive Surgery: New Officers are as follows: Bernice Z. Brown, president; Arthur S. Grove, president-elect; John A. Burns, vice-president; Daniel L. McLachlan, executive secretary; George L. Paris, treasurer; William R. Nunery, secretary; Paul T. Gavaris, program chairman; Bradley Lemke, assistant program chairman; and Clinton D. McCord, Jr., immediate past president and chairman of the advisory committee.

Research to Prevent Blindness: Senior Scientific Investigators

Research to Prevent Blindness announced four Senior Scientific Investigators. They are Robert E. Anderson, Department of Ophthalmology, Baylor College of Medicine; Robert L. Church, Department of Ophthalmology, Emory University; Peter Gouras, Department of Ophthalmology, Columbia University; and Wayne L. Hubbell, Department of Ophthalmology, University of California, Los Angeles.

Personal

Nicholas T. Iliff

Nicholas T. Iliff has been named full-time director of the oculoplastics service at the Wilmer Eye Institute, Baltimore.